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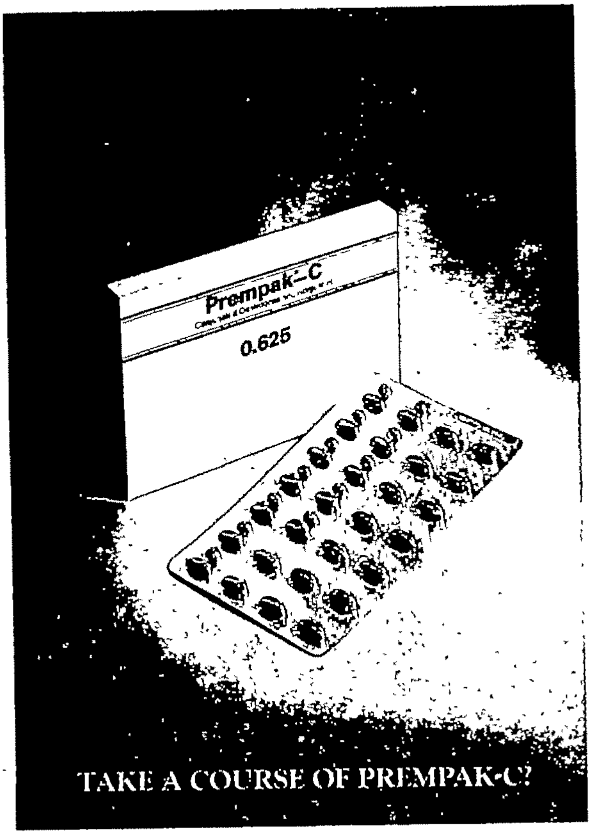

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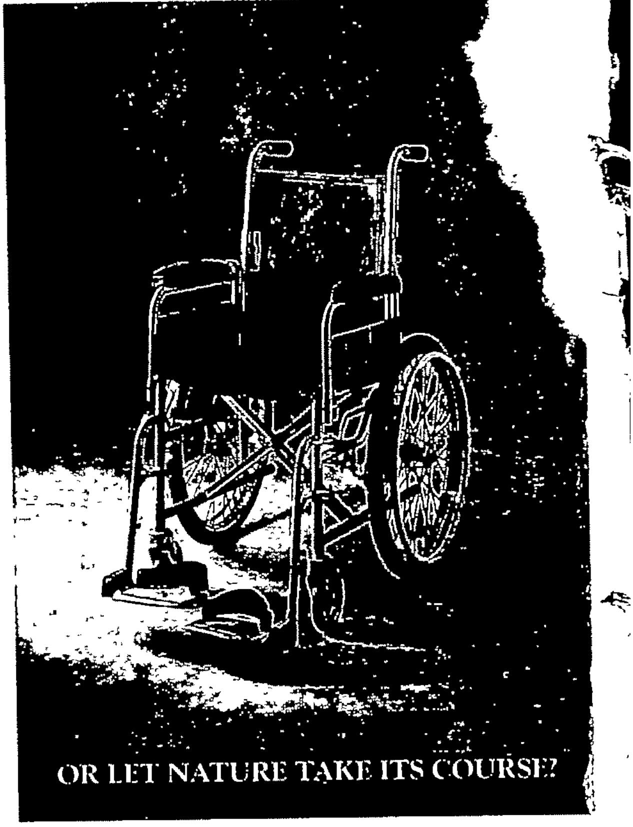

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COMMENTARIES

Gamete donation and anonymity

On 1 November 1990, the Human Fertilization and Embryology Bill (1989) received royal assent. Its eventual passage through both Houses into statute followed a decade of public debate, which was frequently heated and sometimes acrimonious. The most telling contribution to this discussion was the publication in (1984) of the report of the Warnock Committee (DHSS 1984) upon which the subsequent legislation was to be largely based. This eventually came about because, in the Lord Chancellor's words, 'there is a broad censensus about the need for legislation on embryo research so that it can be properly brought under statutory control'. The act will, however, cover many other important areas of reproductive practice, including gamete donation. Children born as a result of the donation of either a sperm, egg, or embryo will be recognised as the children of the recipient couple, and the status of the couple and the child as well as the responsibilities of the donor will now be defined by the law.

Not all aspects of gamete donation are, however, covered by the act, and it is probable that there will be continuing discussion about secrecy and anonymity, as well as the needs and rights of the children. The paper by Oskarsson *et al.* in this issue is a contribution to this debate. The difficult question of anonymity among oocyte donors has vexed the interim Licensing Authority to the extent that they have published an information booklet on the topic, and have recently re-affirmed their view that egg donors should remain anonymous (the Fifth Report, Interim Licensing Authority, 1990). However, not all would agree with this.

Oocyte donation is now an established procedure likely to result in pregnancy at least as often and possibly more frequently than with standard in vitro fertilisation and embryo transfer (IVF-ET). There are many reports describing successful outcomes and the techniques have been reviewed recently (Cameron *et al.* 1989; Bromwich, 1990). It is inevitable that the demand for treatment will increase and that the indications for treatment will widen as time goes by. Present indications include premature ovarian failure and genetic disorders. Ovarian failure can occur spontaneously or after radiotherapy or chemotherapy. The latter category presents a particular need as it can now be expected that more than 50% of young women being treated for lymphoma will be cured, but with a high chance of resultant ovarian failure (Ratcliffe *et al.* 1990).

However, there remains a major problem of supply and demand. Clearly the most suitable eggs would be those surplus to requirement in an IVF programme but, with the increasing availability and success of embryo cryostorage, particularly at the zygote stage (Fugger 1989), most couples would prefer to have the oocytes fertilized and the embryos cryopreserved for their own future use. Oocyte cryostorage might provide some flexibility in this respect, but techniques are not yet available that provide acceptable results. Nonetheless, there is much work in this area at present and, although some workers are pessimistic (Trounson & Kirby, 1989), it does seem likely that progress will be made eventually (Surrey & Quinn 1990). In the absence of spare eggs, couples seeking oocyte donation will become increasingly dependent on volunteer donors. These can be women having sterilization procedures who are willing to have superovulation and oocyte recovery, a method that has already facilitated much research work (Templeton *et al.* 1984 & 1986; Braude *et al.* 1984). Alternatively, they can be true volunteers willing to undergo the hazards of ovulation induction and oocyte recovery for altruistic (Power *et al.* 1990) or other reasons. This is clearly a difficult area, legally and ethically, particularly if any form of inducement is offered. In practice, however, volunteer egg donors can be relatives or friends of recipient couples (Sauer *et al.* 1989a), and this factor brings into the discussion the desirability (or not) of anonymity in gamete donation.

Oskarsson *et al.* asked 234 couples having IVF about their attitudes to sperm and egg donations. Generally, couples approved both sperm and egg donation for clinical and research purposes, confirming the results of previous surveys. Of the couples willing to donate oocytes, almost half said they would do so even if their name was made available to the recipient. The same question regarding sperm donation was not asked, but had it been, several recent studies suggest it would have had a very different response (Handelsman *et al.* 1985; Sauer *et al.* 1988; Daniels 1988; Sauer *et al.* 1989b). In this country, sperm donation has characteristically been anonymous and this has apparently suited both donors and recipients, the latter being particularly concerned with secrecy. The attitude of the resultant children though, were they to learn of their genetic origin, remains a matter of great concern. This particular issue, among others, weighed heavily enough in the formulation of the new legislation that a central registry of donors is to be established. Children born after gamete donation will have access to the registry and to a reasonable amount of non identifiable medical and social information. They will, for example, be in a position to ask whether they are in any way related to their prospective partner, although assurances have been given that the name of the donor will never be divulged, even were the legislation to change at some future date. The extent to which this development will affect donor recruitment remains to be seen, but difficulties, or at least a change in the characteristics of donors, can be expected.

However, there does appear to be a marked difference in attitudes to sperm and egg donation, although there is considerable concurrence between the donors and recipients in each case. By and large sperm donors wish to remain anonymous and the recipients feel that secrecy is important. On the other hand, oocyte donors are more likely to be prepared to be identified (Power *et al.* 1990), and recipients are less anxious about anonymity, particularly if the donation comes from a sister. Although these differences may appear to reflect greater male sensitivity about reproduction, they are perhaps not too surprising. In the case of egg donation, the woman experiences the pregnancy and birth, the child is, in effect, her own and this is now recognized within the law. On the other hand the male partner of a couple having sperm donation has contributed nothing, besides his permission, and despite his subsequent role as father and protector, again now recognised within the law, may nonetheless feel vulnerable to the possibility of others knowing that the child is not his. Although some of the issues arising from these circumstances are now controlled by statute, much more research and discussion is needed: not least involving the attitudes of the resultant children, whose particular needs are most likely to be ignored. The issue of secrecy is most likely to affect the subsequent relationship between parents and child, while the slightly different issue of anonymity introduces a relationship with a third party, the donor. In many ways it would be preferable if non-anonymous gamete donation was more acceptable to our society, as the present cloak of secrecy inhibits free discussion and falsifies relationships. Further public debate may clarify our priorities here and help us identify those things in our family life that we value most.

In the meantime there seems to be no rational reason why non-anonymous oocyte donation should not be permitted, and indeed encouraged, as it reflects a healthy attitude of openness which may ease future difficulties in relationships. The new Human Fertilization and Embryo Authority should continue to examine this question.

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Obstetric mortality and its causes in developing countries

Through its charter as a Commonwealth College the Royal College of Obstetricians and Gynaecologists (RCOG) has a dual responsibility; a national role reflected in improving standards of obstetric care at home (there were 2500 maternal deaths in 1929, the year the College was founded compared with fewer than 150 today), and an international role supported through sister institutions in the Old Commonwealth and standing committees of fellows and members in other countries.

Despite advances made during the past 50 years, there is a widening gap between obstetric standards in this country and those in the developing world.

Fellows and members of our College have as junior colleagues overseas doctors who come to this country for postgraduate experience; some are invited to teach, examine or organize workshops abroad. Sadly, much that we offer to overseas candidates is irrelevant to practice in the countries they come from, and there is increasing unease that we are providing unsuitable training for young professionals who will become opinion leaders in their own countries.

The meeting generously supported by 'Birthright', which was held at the RCOG in June 1989 reflects College concern in this matter. The published proceedings of this meeting (Bullough *et al.* 1990) have a message for us all.

Aggregated reports on maternal mortality indicate annual global losses of more than 500 000 women in addition to often severe and disabling morbidity; 99% of these deaths occur in the Third World. An overall maternal mortality of 400/100 000 prevails in the developing world, ranging up to 1500/100 000 in some Subsaharan regions, compared with mortalities in Western Europe as low as 6/100 000.

Even these terrible figures may underestimate the problem. Notification procedures are notoriously unreliable, indirect causes and late puerperal deaths are overlooked, and vital events in the home, unrecorded by the health system, may rely on fortnightly reports from an unlettered village watchman to a distant police post.

Perinatal death rates, that most sensitive index of maternal care, are not recorded at national level. Isolated field studies in the Indian subcontinent suggest rates of 60 to 70/1000 (Barns 1989).

Obstetric practice in these countries is reminiscent of the 19th century. Deaths occur frequently from haemorrhage, sepsis, eclampsia, obstructed labour and its sequelae, illegal abortion, viral hepatitis and anaemia. There is an underlying synergistic background of malnutrition, infection and unregulated fertility, combined with inadequate obstetric care and ineffective public health services, affording little protection during pregnancy and delivery against an uninhibited stream of parasitic, viral and bacterial infections coming from the environment.

Poverty, time honoured dietary restrictions and harmful birth practices, a deeply embedded preference for the untrained services of traditional midwives, adherence to indigenous remedies and ethnic, genetic and geographical factors combine to increase pregnancy risks. Underlying this is a clearly demonstrable correlation between female literacy, education and maternal mortality (Rao 1985). Thus maternal death must be viewed as the outcome of a chronic socio-obstetric disease process.

Obstetric services

There are still many areas where most deliveries are assisted by traditional birth attendants (TBA) or are self delivered or attended by another member of the family. Poor quality of care and difficult access to care overshadows all other factors contributing to obstetric mortality. Improvement depends on redeployment and replanning services within existing fiscal limits, combined with health education for women in self surveillance.

Organized services in these countries are at three levels; central specialist hospitals, smaller first referral institutions with facilities for caesarean section, and peripheral health centres and subcentres at primary level. Outside this system is a community based health function provided by the TBA. Distances between these levels are magnified by inadequate transport and communication.

Access to obstetric care at first referral level is regarded as the key to the situation. Although not susceptible to global measurement, Asian sample studies have revealed that up to 40% of women may die in childbirth without contact with any level of care, a further 8% dying while in transit (WHO 1986) and 15% arriving moribund at referral centres (Rao 1975; 1978–81).

These various aspects of Third World obstetric care, as well as the significance of specific local pathology, illegal abortion, tropical anaemias, haemoglobinopathies, viral hepatitis, poor fetal growth and the role of the partogram in difficult labour etc. were fully examined during the course of a meeting in 1989 at the RCOG. Abstracts of the discussions are published (Bullough *et al.* 1990) and verbatim recordings are available on tape from the College.

International health strategies

At an international level, the World Health Organization (WHO) has since 1983 belatedly confronted the problem that, despite the massive investments it has made during the past 20 years in promoting national integrated maternal, child health and family planning, assisted by its sister agencies UNICEF, UNFPA, and FAO, the unacceptable levels of maternal mortality in these countries persist virtually unchanged.

WHO has set member countries the target of halving Third World maternal mortality by the year 2000 and is designing a strategy involving an ambitious training programme for fielding 25 000 obstetric teams in less developed regions of Latin America, Africa and South Asia.

These obstetric teams will comprise a nurse/midwife, community health staff, an administrator and a physician, whose obstetric function is expanded into a team leader responsible for training, supervision and deployment of staff.

The training of midwives, patterned on the developed world, is inappropriate to the innovative managerial and clinical skills required of them in developing countries. Extension of the nurse/midwife's role, which will enable her to perform 'life saving' measures on her own initiative, is being recommended (WHO 1987) and the WHO is supporting such broader midwifery training in a number of countries.

In a paper exercise, the WHO predicts that primary level care as outlined above could diminish what is termed 'the natural maternal mortality rate' by 20%, and if linked with first referral facilities might lower it by 80%.

A joint, WHO/FIGO Task Force (1989) has suggested that all national obstetric and gynaecological organizations should promote training curricula that relate more closely to obstetric needs at primary and first referral level, support training programmes for TBAs foster operational field research into service delivery problems and, through dialogue with the media and women's organizations, advance health education of the public in self care for safe motherhood.

Preventive care, antenatal screening and elective referral of high risk pregnancies for anticipatory care at first referral level institutions or at peripheral centres, is recommended as a general strategy for giving special attention to those in greatest need within a framework of improved care for all. It is suggested that community resources are also enlisted by training indigenous midwives to function as an extension to the health team, with responsibility for screening and referral of 'high risk' categories, distribution of iron and haematinics, antenatal care and home delivery of routine cases, reduction of sepsis by handwashing and clean delivery, and postpartum promotion of family planning (since 1984, three months instruction has been given to 500 000 TBAs in an Indian Government training programme).

In some countries the value of screening is compromised by the prevalence of risk factors in up to 40% of pregnant women; screening policies are therefore a charade unless effective emergency measures are also available at primary level when they are needed (Essex 1978).

Problems of transport and communication, often exacerbated by family reluctance to permit the transfer of the woman to hospital, are serious obstacles to linkage between primary and first referral level care. Although serious obstetric problems arising in the community have to be dealt with at a centre of first referral, the obstetric staff at such centres have neither the influence nor responsibility for framing obstetric policies for their community, and there are usually no formal links between them and health centres at primary level, which they are neither required to visit for consultation, nor provide with mobile support in an emergency.

The role of the College

For the College to fulfil its Commonwealth commitment in concert with steps being taken at international level, it has been recommended that there should be sponsored training in this country, for overseas graduates offering appropriate instruction in local postgraduate centres and a Diploma course, run in conjunction with the Liverpool School of Tropical Medicine, which would advance expertise in health service organization, epidemiology, neonatal health, family planning, nutrition, risk assessment, training of paramedical staff, health team management, and allied subjects.

Such a course would serve three categories of postgraduate: (i) overseas doctors before returning home; (ii) doctors from developing countries responsible for maternal health programmes, and (iii) graduates from this country and elsewhere in Europe who are preparing to work in developing countries.

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Management of retained placenta by umbilical vein injection

Retained placenta is one of the most serious complications of childbirth and if left untreated, maternal death may follow from haemorrhage or infection. Furthermore, the conventional treatment for retained placenta, 'manual removal', which is usually performed in hospital under general anaesthesia or epidural block (Whitfield 1981), is not without risks. Manual removal may result in haemorrhage, infection, rupture of uterus, trauma to the cervix or vagina, and complications of anaesthesia. Because of the complications both of retained placenta and its standard treatment, any management simple and safe enough to be performed at the place of delivery, which reduced the need for transportation and manual removal would be of major benefit to women world-wide. There is some evidence that injections into the umbilical vein, particularly those using a solution containing oxytocin, may reduce the need for manual removal of the placenta (Elbourne 1990).

Injections into the umbilical vein were first described more than 150 years ago by B. Mojon and F. Asdrubali (cited by Koerting 1926). Other authors have reported the use of intra-umbilical vein injection of saline in volumes varying from 200 to 400 ml (Gabaston 1914; Jarcho 1928). Recent studies have reported using smaller volumes of a solution of oxytocin. Although some of these studies have been uncontrolled (Neri *et al.* 1966; Golan *et al.* 1983 & 1984; Heinonen & Pihkala 1985; Hauksson 1986), nine controlled trials have now been reported. The methodological quality of the trials is generally good, although all are small.

Three of the nine trials have assessed prophylactic injections into the umbilical vein in an attempt to reduce the risk of retained placenta (Chestnut & Wilcox 1987; Young *et al.* 1988; Reddy & Carey 1989). The timing of injection ranged from immediately after cord clamping, to 5 min after delivery. The data are too few to provide any reliable indication of the usefulness of this prophylactic strategy.

Six controlled trials have assessed the use of umbilical vein injections for the treatment of retained placenta (Selinger *et al.* 1986; Hansen *et al.* 1987; Kristiansen *et al.* 1987; Frappell *et al.* 1988; Wilken-Jensen *et al.* 1989; Thiery 1990). The upper time limit for defining 'retained placenta', ranged between 15 and 30 min after the birth of the baby. A dose of 10 IU of oxytocin

Table 1. Effect of umbilical vein oxytocin infusion vs 'other management' on manual removal of placenta

Study	Experimental *n* (%)	Control *n* (%)	Odds ratio (95% CI)
Selinger *et al.* (1986)	9/15(60)	8/15(53)	1·30 (0·31 to 5·38)
Frappell *et al.* (1988)	14/22(64)	15/19(79)	0·49 (0·13 to 1·84)
Hansen *et al.* (1987)	14/32(44)	20/28(71)	0·33 (0·12 to 0·91)
Kristiansen *et al.* (1987)	10/19(53)	16/32(50)	1·11 (0·36 to 3·41)
Thiery (1990)	9/19(47)	10/13(77)	0·31 (0·07 to 1·25)
Wilken-Jensen *et al.* (1989)	5/19(26)	11/18(61)	0·25 (0·07 to 0·91)
Typical odds ratio			0·50 (0·30 to 0·83)

was used in all the studies except one (Wilken-Jensen *et al.* 1989), in which 100 IU was used. All the trials used 20 ml of saline solution except for Kristiansen *et al.* (1987) and Wilken-Jensen *et al.* (1989) who used 10 ml and 30 ml, respectively.

Table 1 shows the results of the six trials in which umbilical vein oxytocin injection has been compared either with umbilical vein injection of saline solution (Selinger *et al.* 1986; Frappell *et al.* 1988; Hansen *et al.* 1987; Kristiansen *et al.* 1987; Wilken-Jensen *et al.* 1987) or with 'expectant' management (Kristiansen *et al.* 1987; Thiery 1990). The available data suggest that the treatment of retained placenta with intra-umbilical vein injection of oxytocin is associated with a reduction in the use of manual removal of the placenta (typical odds ratio 0·50, 95% confidence interval 0·30–0·83). The trials provide no strong evidence of any adverse effects of the umbilical injection of oxytocin, although Thiery (1990) has suggested that it may make subsequent manual removal of placenta more difficult.

On the basis of these data, umbilical vein injection of oxytocin seems a promising treatment for retained placenta, but the evidence is not strong and questions remain. For example, are there independent effects of the oxytocin itself and the bolus of fluid in which it is delivered to the placenta? Large randomized controlled comparisons of alternative policies for umbilical vein injection are now needed so that the benefits suggested by the evidence currently available can be either confirmed or refuted, with confidence.

At least one such trial, involving 10 centres in Latin America, is now under way (Carroli 1990).

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Attitudes towards gamete donation among couples undergoing in vitro fertilization

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Summary. The attitudes of 234 anonymous couples undergoing in vitro fertilization toward sperm and oocyte donation were explored by questionnaire. All the questionnaires were returned of which 222 (95%) were complete and analysed. A high proportion of couples found the use of donor sperm acceptable for therapeutic, diagnostic and treatment purposes (77%, 90% and 97% respectively) and 72%, 84% and 90% respectively were willing to donate oocytes for these purposes. Of potential oocyte donors 41% would agree to nonanonymous donation, 12% would wish to meet the recipient couple and although only 4% wanted to choose the recipient, a quarter of the couples would prefer a relative or friend as the recipient. Provision of nonidentifying information about the donor to the recipient couple was acceptable to almost 70% whereas 40% found giving the same information to the child acceptable.

Gamete donation has achieved an increasingly important role amongst the accepted methods of assisted reproduction. Although the use of donor sperm for the treatment of male infertility has been practised at least since 1884 (Phillip 1979), legislation on the rights and duties of the donor, recipient and child has still not been passed in this country.

Oocyte donation is a more recent medical procedure. The first clinical pregnancy after egg donation was reported by Trounson *et al.* (1983) and the first successful pregnancy following such a procedure a year later (Lutjen *et al.* 1984). Parliament has now, however, passed the Human Fertilization and Embryology Act (1990), where these and other issues in the Warnock Report (DHSS 1984) are addressed.

The purpose of this paper is to report the attitude of infertile couples undergoing in vitro fertilization (IVF) towards various issues related to gamete donation.

Subjects and methods

A questionnaire was designed to assess, on an anonymous basis, the attitudes of 235 consecutive couples undergoing IVF at Hammersmith Hospital between July and October 1989 towards sperm and oocyte donation. The answers represent the joint opinion of the couple. The questionnaires were handed out to all women undergoing embryo transfer and com-

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Table 1. Social characteristics of respondents ($n = 222$)

	Number	%
Age (years)		
Under 20	0	0·0
20–24	1	0·5
25–29	21	9·5
30–34	94	42·3
35–39	97	43·7
Over 40	9	4·0
Marital status		
Married	212	95·5
Not married	6	2·7
Divorced	4	1·8
Ethnic origin		
White	198	86·5
Black	10	4·5
Asian	14	6·3
Other	4	1·8
Religion		
Roman Catholic	42	18·9
Protestant	119	53·6
Other religion	39	17·6
No religion	22	9·9
Children		
None	164	73·9
1–2	57	25·6
More	1	0·5
Education		
None	2	0·9
Primary	13	5·9
Secondary	139	62·6
College/Diploma	38	17·1
University	30	13·5

pleted during their 2-h bed rest at the hospital after embryo transfer. Anonymity was assured and it was made clear that the answers carried no obligations or implications for the present or future treatment of the couple.

The couples were asked to record social characteristics such as age, marital status, ethnic origin, religion, number of children and education. They were asked to report their attitude towards sperm donation for treatment of male infertility, for the diagnosis of infertility, and for research purposes. They were also asked if they were willing to donate eggs anonymously to another woman, and for diagnostic or research purposes. All couples were asked whether egg donors should be paid and if they would want to know about the donor had they themselves been conceived by a donor gamete.

Those who expressed a willingness to donate eggs to another woman were then asked if they would do so nonanonymously, if they had any preference with regard to selection of, or contact with, the recipient, whether nonidentifying information about the donor should be available to the recipient couple or child, and if the donor should have access to similar information on the recipient couple.

Ample space was provided after each section of the questionnaire and the couples were encouraged to express their views freely. The questionnaires were returned in a sealed envelope and analysed at the end of the study period, using the χ^2-test for statistical analysis where appropriate.

Results

All the questionnaires which were handed to 234 consecutive IVF couples were returned, of which 222 (95%) were complete and analysed. The remaining 12 (5%) were incomplete or ambiguous and therefore excluded from the analysis. Of the 234 couples 11 (5%) needed donor sperm and none used donated oocytes during their IVF treatment.

Social characteristics (Table 1)

Most of the respondent-couples were white, married and aged between 30 and 40. Just over half were Protestants and equal proportions were of Roman Catholic and other religions (19 and 18% respectively). A quarter of the couples had children and 31% had received more than secondary school education.

Attitudes to sperm donation (Table 2)

Just over three-quarters found sperm donation acceptable whereas over 90% agreed to the use of sperm for diagnostic and research purposes. Over half (52%) would not want to know about the donor if they themselves had been conceived by donor sperm.

Further comments on sperm donation were made by 22 couples (10%). Three stressed the importance of matching donor and recipient. Two couples commented on availability of nonidentifying information about the donor, two on agreement to research if it did not involve fertilization of eggs and two couples found the use of sperm acceptable generally but not personally. One patient was only in favour of donating sperm for relatives or close friends of the donor.

Table 2. Attitudes towards sperm donation ($n = 222$)

Question	Answer	Number	%
Do you find the use of donated sperm acceptable for treatment of male infertility?	Yes	172	77·4
	No	25	11·3
	Unsure	25	11·3
Do you find the use of donated sperm in order to diagnose infertility acceptable?	Yes	200	90·1
	No	10	4·5
	Unsure	12	5·4
Would you find the use of donated sperm for research purposes acceptable?	Yes	215	96·8
	No	4	1·8
	Unsure	3	1·4
If you had been conceived by donor sperm, would you want to know about the donor?	Yes	56	25·2
	No	116	52·3
	Unsure	50	22·5

Three couples expressed their objection to sperm donation to unmarried women and for the purpose of profit making and genetic engineering.

Attitudes to oocyte donation (Tables 3 and 4)

Of the 222 couples, 160 (72%) said they would be willing to donate eggs anonymously to another woman and almost 90% would be prepared to donate eggs for research purposes. Four couples commented that egg donation should be widely available even within the National Health Service.

Three said they would only donate oocytes if they themselves had achieved a pregnancy first and one couple expressed a determination to donate eggs, as a separate procedure, after they had achieved a pregnancy.

Only three couples expressed the view that donors should be paid but another five commented that necessary travel expenses should be covered. Another two stated that they were only in favour of egg donation where profit making and genetic engineering were not the incentive

Similar to attitudes towards sperm donation, over half of the couples (52%) would not want to know the donor if they themselves had been conceived by a donor egg.

Of the 160 couples willing to donate oocytes, 66 (41%) said they would do so even if their name was made available to the recipient. One couple, however, stated that they would want no further contact with the recipient.

Whereas half the couples (51%) had no objections to donating eggs to the single woman, very few showed an interest in meeting or choosing the recipients (12 and 4% respectively). Just

Table 3. Attitudes towards oocyte donation ($n = 222$)

Question	Answer	Number	%
Would you be willing to donate eggs anonymously to another woman?	Yes	160	72·1
	No	34	15·3
	Unsure	28	12·6
Would you donate eggs for the purpose of diagnosing the cause of infertility in another couple?	Yes	186	83·8
	No	14	6·3
	Unsure	22	9·9
Would you be willing to donate eggs for research purposes?	Yes	199	89·6
	No	10	4·5
	Unsure	13	5·9
Should egg donors be paid?	Yes	3	1·4
	No	185	83·3
	Unsure	34	15·3
If you had been conceived by a donor egg, would you want to know about the donor?	Yes	55	24·8
	No	116	52·2
	Unsure	51	23·0

Table 4. Attitudes of couples willing to donate oocytes ($n = 160$)

Question	Answer	Number	%
Would you donate eggs to another woman if your name was made available to her?	Yes	66	41·3
	No	48	30·0
	Unsure	46	28·7
Would you object if your egg(s) were donated to a single woman?	Yes	50	31·3
	No	81	50·6
	Unsure	29	18·1
Would you wish to meet the recipient couple?	Yes	19	11·9
	No	110	68·8
	Unsure	31	19·3
Would you wish to choose the recipient couple	Yes	7	4·4
	No	137	85·6
	Unsure	16	10·0
Would you prefer to donate to a relative?	Yes	43	26·9
	No	91	56·9
	Unsure	26	16·2
Would you prefer to donate to a friend?	Yes	46	28·7
	No	84	52·5
	Unsure	30	18·8
Should nonidentifying information* about the donor be available to the recipient couple?	Yes	111	69·4
	No	25	15·6
	Unsure	24	15·0
Should nonidentifying information about the donor be available to the child?	Yes	64	40·0
	No	59	36·9
	Unsure	37	23·1
Should nonidentifying information about the recipient couple be available to the donor?	Yes	57	35·6
	No	73	45·6
	Unsure	30	18·8

* Physical characteristics, age, education, occupation, etc.

over a quarter would prefer to donate to a relative (27%) or a friend (29%).

More than two thirds (69%) were in favour of providing nonidentifying information about the donor to the recipient couple but just over a third were in favour of giving similar information to the child (40%) or information about the recipient couple to the donor (36%). One couple pointed out that nonidentifying information might be tantalizing rather than satisfying.

Other comments related to the future emotional aspects of donors, recipients and children (three patients) and the difficulty in assessing how they might respond to the different aspects mentioned in the questionnaire.

Attitudes among different religious groups did not differ significantly for any of the questions except that among couples who were willing to donate oocytes, those professing 'other religion' wished to meet the recipient couple significantly more often when compared with the rest of the study population (33% (7/21) *vs*, 7% (10/140); $\chi^2 = 9{\cdot}18$, $P = 0{\cdot}002$).

There was, however, a trend in this group towards lower acceptance for sperm donation (54% (25/39)) and oocyte donation (64% (21/39)), but increased tolerance for making their name known if they became donors, when compared to the other groups (52% (11/21) *vs* 39% (55/140)).

In comparison with the groups professing a religion, the 22 couples with no religion also showed a trend for more frequently wanting to know about the donor if they themselves had been conceived by donor gametes, higher acceptance for donating to single women, less preference for donating to relatives or friends and increased support for revealing nonidentifying information to all parties.

No other social characteristics showed any influence on the answers.

Discussion

As the issue of gamete donation has recently been under scrutiny in Parliament who have now passed the Human Fertilization and Embryology Act (1990) the view of the infertile couples should be taken into account.

This study reports the attitudes on sperm and oocyte donation of 222 consecutive IVF couples treated at Hammersmith Hospital between July and October 1989. Although this was a group with longstanding infertility only 5% had benefited directly themselves from gamete donation.

A high proportion of couples found the use of donor sperm acceptable for therapeutic, diagnostic and research purposes (77%, 90% and 97% respectively). A comparable proportion were willing to donate eggs for the same purposes (72%, 84% and 90% respectively). To our knowledge, attitudes on these issues in Britain have not been explored before. In Australia, opinion polls published in 1983 showed a significant acceptance of sperm and egg donation (56% and 57% respectively) (Roy Morgan Opinion Poll 1983). However, in another Australian study (Burton *et al.* 1986), a smaller proportion of IVF patients were willing to donate excess oocytes for treatment (33%) or research (43%). Among 1400 respondents who completed a woman's magazine questionnaire in New Zealand, 64% were in favour of using donor sperm in IVF and 61% donor oocytes (Daniels, unpublished data). In France, Junca *et al.* (1988) found that 50% of their IVF patients agreed to donate oocytes to another sterile woman.

Our survey shows that, among those willing to donate oocytes, although only 4% wished to choose the recipient couple, 41% would still donate eggs even if their name was made available to the recipient and just over 25% would, given the option, prefer to donate to a relative or friend. However, only 12% wished to meet the recipient couple. These results are comparable to the findings of Leeton & Harman (1986), where 16 of 34 anonymous oocyte donors stated they would be prepared to donate oocytes to a known recipient. This shows a high level of understanding towards the needs of the recipient couple although most of the couples wished to preserve their privacy and avoid emotional involvement.

Although informing the child conceived by a donor gamete about its origin is currently at its parents discretion, it is of interest to note that more than 50% of our IVF couples would not have wished to know about the donor had they been conceived by a donor gamete themselves, although 25% would want to know. Daniels (1988) reported that 41% of sperm donors and recipients felt that the child should not be told about the nature of its conception.

Where disclosure of information about the donor's identity was acceptable to only 41% of the couples willing to donate oocytes, disclosure of nonidentifying information was accepted by 69%. It is likely that the unclear legal position of the donor has an important influence on these attitudes, although the position of sperm donors has now been clarified. This is in agreement with the findings of Handelsman *et al.* (1985) among semen donors. We found 40% of couples in favour of revealing nonidentifying information to the child; this is similar to previous findings among semen donors (Daniels 1988).

In 1985, Sweden was the first country in the world to have a comprehensive legislation on artificial insemination (Ewerlöf 1985). The new law decreed that, in order to safeguard the child's best interests, donor anonymity was no longer acceptable.

This contrasts with current practice in Britain, where total anonymity is maintained, with no attempt to obtain full biographical information about the donors. Such background knowledge is therefore unavailable to the recipients and the resultant child(ren). It should be noted that this approach does not accord with our respondants, 69% of whom felt that nonidentifying information should be available and 41% of whom would accept a relationship in which donors and recipients were known to each other. The legislation, recently before Parliament, recommends that a central register of donors and recipients be maintained but, unlike the Swedish law, makes no requirement for biographical or identifying information to be made available.

The questions posed to the IVF couples in our study effectively illustrate the complexity of the social, emotional, ethical and legal issues faced by those who consider gamete donation. The need for careful and focused counselling is made clear as much by the wide divergence of views expressed, as by the significant proportion of couples who felt unsure of how to deal with such fundamental dilemmas, touching not only upon their own needs and rights,but those of children and donors too.

Further to the established practice of artificial insemination, oocyte donation has become a viable option for women who are unable to provide genetically suitable oocytes. Although common ethical and legal issues apply to sperm and oocyte donation, the inaccessibility and scarce numbers of oocytes poses a certain problem.

Further research is needed to improve our knowledge of the psychological and social implications of gamete donation.

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A multi-centre collaborative study into the treatment of menorrhagia by Nd-YAG laser ablation of the endometrium

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Abstract

Objective—To determine the safety and clinical effectiveness of Nd-YAG laser ablation of the endometrium in the treatment of menorrhagia
Design—A prospective 3-year observational multi-centre study.
Setting—Gynaecological units in the UK and USA with special interest in endoscopic laser surgery.
Subjects—859 women with menorrhagia resistant to medical therapy.
Main outcome measure—Duration of laser ablation, intra- and post-operative complications, amenorrhoea rate, oligomenorrhoea rate, and woman's subjective assessment of treatment.
Results—No major complications occurred in 859 treatments. Four (0·4%) cases of transient fluid overload, 4 (0·4%) of infection, and 3 (0·3%) of uterine perforation occurred. Each of the perforations occurred during insertion of the rigid instruments and none was produced by the laser. There were no major haemorrhages, no blood transfusions were needed, and no woman required a laparotomy. The mean duration of the laser ablation was 24 min, and the average stay in hospital was <24 h. Of the 479 women followed up for at least 6 months after treatment 288 (60%) developed complete amenorrhoea and 152 (32%) reported continuing but satisfactorily reduced menstruation; 39 (8%) failed to improve with the first treatment, but 26 of them responded to a second laser ablation. Overall 466 (97%) had a satisfactory response to laser ablation and only 13 (3%) required subsequent hysterectomy.
Conclusion—Endometrial laser ablation would appear to be a popular, safe, effective and economical alternative to hysterectomy for the treatment of menorrhagia.

There has been increasing interest in various hysteroscopic alternatives to hysterectomy for the treatment of menorrhagia. The endometrium can be selectively destroyed to relieve troublesome menstrual symptoms whilst conserving the bulk of the surrounding healthy uterine tissue. Such minimal invasive hysteroscopic surgery can be performed using electrical (Magos *et al.* 1989; Vancaille 1989), laser (Goldrath 1989), or radiofrequency energy (Phipps *et al.* 1990). These techniques may offer major potential clinical benefits but may also be associated with significant potential complications. Their safety and efficacy in routine clinical practice are not yet established (Garry 1990). This large collaborative study from two centres in the

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UK and one in the USA seeks to determine the clinical effectiveness and safety of one of these procedures, endometrial laser ablation (ELA).

Patients and methods

A common entry protocol was agreed. The procedure was offered to women who fulfilled our standard indications for hysterectomy for the treatment of menorrhagia. They all suffered from distressing or disabling menorrhagia which was resistant to medical treatment. All had preoperative assessment of the endometrium with either diagnostic curettage, or hysteroscopic inspection and endometrial sampling. Those with endometrial atypical hyperplasia and established malignancy were excluded as were women with major uterine fibroids or endometriosis. The aim was to treat dysfunctional uterine bleeding but women with small sub-mucous uterine fibroids of less than 2 cm diameter were not excluded. A subgroup of patients with a variety of severe medical problems including renal and liver transplants, chronic renal failure, coagulopathies, gross obesity and other conditions that make conventional hysterectomy hazardous were included in the study.

All the women had completed their families and all were aware of the permanent effect of the procedure on their future child-bearing potential. Fully informed consent was obtained and the procedure was approved by the relevant ethical committees.

A total of 859 patients were enrolled from three centres, Orpington and Middlesbrough in the UK and Princeton, USA. The mean age of the women was 39 years (range 21–54 years). The severity of the menstrual losses was assessed subjectively by the patient describing and charting the length and frequency of the flow and the number and type of sanitary protectives required. All the women had a general clinical assessment, a pelvic examination and had recently had normal cervical cytology.

All women were given pre-operative medication to produce a thin atrophic endometrium. The drug of choice was danazol given in a dose of 600 mg daily for at least 4 weeks. Occasionally this drug could not be tolerated and those women were given a progestogen or buserelin in the UK or luprolide acetate in the USA.

All the operations were performed by the three authors of this paper. All procedures in the UK were performed under general anaesthesia as were most of those in the USA. Increasingly in the USA women are offered the option of having the procedure performed under local paracervical block and intravenous sedation. There has been a steady increase in the number choosing such a local anaesthetic option, and 40 of the last 50 women chose this. Most found this approach satisfactory but a proportion experienced some discomfort and 5% required supplementary general anaesthesia.

All the procedures in the USA were performed in a surgi-centre setting and all were day cases. In the two centres in the UK most women stayed overnight but, as confidence in the technique is growing, women are now more and more being allowed home the same day. Factors influencing same day discharge include speed of recovery from the anaesthetic, distance from home, and social circumstances. Women with excessive fluid absorption are retained overnight to monitor urinary output but they are invariably 'in balance' within 24 h. No woman discharged as a day case has been readmitted within 24 h and there has been no recorded morbidity associated with early discharge.

In each centre a rigid 30 degree operating hysteroscope (Karl Stortz, West Germany or Weck-Baggish, USA) was used. The uterine cavity was distended with 0·9% sodium chloride infused under pressure using either a blood pressure cuff (Princeton), or a roller pump (UK). Recently an automatic infusion system (Hamou Hysteromat, Karl Stortz, West Germany) has been introduced into the Middlesbrough protocol with significant improvements in fluid management. A video-system was used on every occasion and the procedures guided by viewing the monitor.

Nd-YAG laser energy was transmitted to the endometrium via a 600 μm flexible quartz fibre which was inserted down the operating channel of the hysteroscope. The Nd-YAG laser used was the SLT CL 60/or CL100 (Surgical Laser Technology, Malvern, US) or a Coopersonic 100. The mean power used was 60 W (range 50–80 W).

The cervix was dilated just enough to accommodate snuggly the operating hysteroscope. The sodium chloride infusion system was connected to the inflow channel of the hysteroscope and the outflow channel connected to a series of graduated containers. This closed system enabled a frequent accurate check of infusion fluid balance. When a clear view was established the endometrium was ablated in a systematic manner beginning at one tubal ostium, moving to the other, treating the fundus and then the anterior, lateral and finally the posterior uterine wall. It was sometimes helpful to rotate the hysteroscope through 180° whilst keeping the camera in a constant position in relation to the patient to complete the posterior wall. Otherwise the hysteroscope was maintained in a constant position and applied to each uterine wall in succession. The bare-fibre dragging technique (Goldrath 1981) was used throughout. The advantage of this technique over the blanching technique described by Lomano (1988) is that the furrows made by the fibre clearly demarcate from non-treated areas and so make it easier to ensure that the whole of the cavity is ablated. The procedure was continued down to the internal os, but care was taken to avoid treating the cervical canal.

Women were seen for follow-up assessment at 4–6 weeks, 3 months, 6 months and then annually. In all the women treated in Orpington, a post-operative pelvic ultrasound was performed and, in America, a repeat hysteroscopic assessment was performed one year after treatment. The clinical outcome was assessed at least 6 months after treatment and follow-up has been continued for up to 3 years.

Results

Of the 859 women in this series 479 were followed for more than 6 months. The mean operating time was 24 min (range 11–90 min), and 99% were sent home within 24 h of treatment. The mean volume of 0·9% sodium chloride used to distend the uterus was 4·6 litres and the mean fluid deficit at the end of the procedure was 1474 ml (range 0–12000 ml).

Intra-operative complications are shown in Table 1. The uterus was perforated on three occasions, a rate of 0·3%. All of these occurred during insertion of the rigid hysteroscope. When this happened the procedure was discontinued, the patient was allowed home within 24 h, and in all three the treatment was achieved uneventfully within 4 weeks. No uterine perforation was caused by the laser, nor was there any case of damage to bowel, bladder or other surrounding structure.

Four women developed (0·4%) symptomatic pulmonary oedema requiring management with post-operative intravenous diuretics. Each responded promptly and all were discharged from hospital within 6–48 h. None of the women had peri-operative bleeding requiring active treatment or blood transfusion. Post-operative pyrexia occurred in four women but only one of these appeared to be associated with chronic pelvic inflammatory disease No woman has developed a haematometra, and none required a laparotomy.

The clinical results assessed at least 6 months after treatment are shown in Table 2. Of the 479 women followed for this time 288 (60%) had developed amenorrhoea and a further 162 (34%) had an acceptable result with a significant reduction in menstrual flow to either a staining or a light normal menstrual period. Overall, 39 (8%) were not sufficiently improved and required a further treatment; 23 of these had a second laser ablation of which 16 were successful, four failed again, and in three their result is not yet determined. One had a third ablation which was successful. Overall 466 (97%) of the women achieved satisfactory control of their menstrual symptoms with one or more laser ablations to the endometrium.

In the Middlesbrough arm of the study a consecutive group of 25 women having an abdominal hysterectomy as treatment for menorrhagia were also assessed and the comparative results are listed in Tables 3 and 4. This small sample was not intended to be a control group but gave some financial details of the cost of a hysterectomy and gave information on morbidity associated with abdominal hysterectomy. These morbidity statistics were similar to those in larger series, published previously (Dicker *et al.* 1982; Grant & Hussein 1984; El Torkey 1990).

Discussion

Goldrath first treated women for menorrhagia with Nd-YAG ablation of the endometrium in 1979 and has recently described his 10 year experience with the procedure (Goldrath 1989). He reported that 93% of these treatments were successful and described only a small number of relatively minor complications. In spite of these encouraging results laser ablation has not yet become an established feature of clinical practice. There have been doubts expressed about the safety of such hysteroscopic techniques (Garry 1990; Lewis 1990; MacDonald 1990) and deaths have been reported in the USA (Baggish & Daniel 1989 a,b). Four deaths following Nd-YAG laser ablation have been described, but in each a coaxial fibre was employed and the fibre

Table 1. Operative details

	Princeton	Orpington	Middlesbrough	Total
Number	342	395	122	859
Operating time (min)	17 (11–27)	27 (17–85)	31 (11–90)	24
Mean fluid deficit (ml)	1500	1500	1300	1474
Complications				
Pulmonary oedema	2	2	0	4
Perforation with hysteroscope	1	2	0	3
Perforation with laser	0	0	0	0
Haemorrhage	0	0	0	0
Infection	0	2	2	4
Haematometra	0	0	0	0
Total				11

or tip was cooled with either carbon dioxide or nitrogen gas. The cause of death in these women was air embolism. No such disaster occurred in our series or the series described by Goldrath (1989). Our technique uses a bare fibre with no coaxial channel and cooling is by external sodium chloride. With the correct application of such a technique, air embolism should be impossible.

Two types of uterine perforation may occur. Those occurring during the insertion of the rigid instruments are familiar to all gynaecologists and if recognized are usually of little clinical importance. The rate of such perforation in this series was 0·3% and the perforations caused no major problems. The second type of perforation is that caused by the ablative element. Such a complication may be associated with a substantial risk of serious damage to surrounding structures. No such problems were encountered in the 859 women treated in this series. By contrast, in a series of 100 electrosurgical resections of the endometrium (Magos 1990), there was a 3% perforation rate during resection requiring laparotomy.

During any endometrial surgery the sub-epithelial blood vessels are inevitably opened with the risk of systemic absorption of the distending medium. Pulmonary oedema occurred in 0·4% of our patients. As the distending medium is physiological, it is relatively easy to treat any fluid overload. Non-physiological fluids such as glycine cause additional metabolic and dilutional problems and might be more difficult to treat. Clinically the patients with fluid overload in our series responded very rapidly to treatment. The use of an automatic infusion system (Hamou Hysteromat) promises to improve the situation further. One of us (R.G.) has recently tried this equipment in 10 consecutive patients and found a fluid deficit of less than 100 ml in 9 (compared with a series mean of 1300 ml).

The clinical outcomes with a 60% amenorrhoea rate and a 97% subjective 'cure' rate are very similar to the rates reported by Goldrath (1989) and indicate that his work is reproducible both in other centres in the USA, and in very different centres in the UK. At present the treatment is intended to produce amenorrhoea in every woman and it is not clear why laser abla-

Table 2. Clinical results

	Princeton	Orpington	Middlesbrough	Total
Number	198	213	68	479
Amenorrhoea	111 (56%)	139 (65%)	38 (56%)	288 (60%)
Reduced menses	74 (37%)	55 (26%)	23 (34%)	152 (32%)
First failure	13 (7%)	19 (9%)	7 (10%)	39 (8%)
Subsequent success	10 (5%)	12 (6%)	4 (6%)	26 (5%)
Hysterectomy	3 (2%)	7 (3%)	3 (4%)	13 (3%)

Table 3. Clinical features of hysterectomy compared with endometrial laser ablation (ELA)

	Hysterectomy	ELA
Time in theatre (min)	88	44
Treatment time (min)	60	31
Mean hospital stay (days)	7	1
Mean convalescence (days)	56	10
Proportion with post-op complications	45%	1%
Post-op pain (<24 hrs)	94%	0%

tion should be more effective in some cases than others. In at least a proportion of failures adenomyosis appears to be the underlying undiagnosed problem. Many women appear to be equally or more content with very scanty but regular menstrual losses than with absolute amenorrhoea. They present with excessive menstrual losses and gynaecologists traditional surgical response is to produce the extreme of amenorrhoea. Perhaps we should be looking at least in some cases to 'normalizing' rather than abolishing menstruation.

Almost all the women left hospital within 24 h of treatment. All women treated in America and a progressively increasing proportion of those treated in the UK were managed as day cases. Endometrial laser ablation (ELA) is a cost effective procedure. A Nd-YAG laser costs between £40 000 and £80 000 depending on make and power. A hysteroscope, video system and fluid management system may cost a further £10 000 and £15 000. This significant capital cost is offset by savings made by reductions in: the duration of the procedure, time needed in theatre, time in hospital, time off work and in the number of post-operative complications (Table 3). These features permit a more efficient use of expensive resources and have allowed an increased throughput. In the first year of using ELA, R.G.'s waiting list for hysterectomy in Middlesbrough fell from 150 to five and the waiting time for any surgical treatment of menorrhagia fell from more than 12 months to 6 weeks. The costs of theatre consumables such as drapes, swabs and suture materials is 45% less for ELA than for hysterectomy (Table 4). Assuming a laser life of 7 years and a patient throughput of 500 procedures per annum such savings alone would pay for the equipment. If this decreased demand allowed for an appropriate reduction in in-patients beds, it is estimated that for every 500 patients treated with ELA rather than hysterectomy there could be a saving of £390 000. The financial benefits would be of an even greater magnitude, if the savings associated with early return to work, and reduced social benefit payments are included. It is expected that the potential financial savings in the USA will be even greater.

This multicentre study is the largest so far reported on the use of Nd-YAG laser for the treatment of menorrhagia, and it appears to confirm the conclusions of Goldrath. In the short term it is safe and effective. There is a need for clinical research to compare the standard treatment of hysterectomy with the various locally ablative techniques that are coming into use. Long term studies are needed to determine if the reduction in menstrual loss is maintained, if there is any occurrence of haematometra and pyometra, and above all if there is any adverse effect on the frequency of endometrial cancer.

The spontaneous age-adjusted incidence of carcinoma of the endometrium in most developed countries varies between 5 and 20 per 100 000 women (Beral 1985). It will consequently require a large, coordinated long-term study to detect even major adverse effects on the incidence of this malignancy caused by the endometrial ablative techniques.

It is unlikely that any unit, which acquires sufficient experience in these ablative techniques, will be able to resist the demands of the patients, and participate in a prolonged randomized study. National and international comparisons

Table 4. Costs of hysterectomy compared with endometrial laser ablation (ELA)

	Hysterectomy		ELA	
Theatre consumables	£58·09		£27·77	
Laser depreciation			£21·42	
Laser fibres			£9·60	
Staff costs	£107·21		£74·07	
Total theatre costs		£165·30		£132·86
Ward costs		£800·00		£50·00
Total costs		£965·30		£182·86

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between the various ablative techniques and between these and the 'gold-standard' treatment of hysterectomy would be more practicable. Common entrance criteria, treatment protocols, and outcome measure could be agreed. These could be collated and a register of adverse outcomes established. This should enable the true value of these procedures to be determined and give the earliest possible warning of any unexpected outcomes. There is an unprecedented opportunity for both sceptics and enthusiasts to collaborate in the assessment of this potentially important new approach to gynaecology.

The introduction of such minimally invasive endoscopic surgery might change dramatically the core content of operative gynaecology. Hysteroscopic and laparoscopic procedures could result in a marked increase in day-case and short-stay surgery with a consequent reduction in standard 'open' surgery with the need for large numbers of in-patients beds. With such large economic, political and clinical issues involved it is important that such revolutionary procedures are properly assessed before being widely introduced. We believe this study supplies some evidence to justify establishing more definitive prospective comparative studies.

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Phospholipase activity in the endometrium of women with normal menstrual blood loss and women with proven ovulatory menorrhagia

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Summary. The activity of phospholipase A_2 types 1 and 2 and phospholipase C was measured in the endometrium of women with ovulatory menorrhagia and in those with normal menstrual blood loss. In both groups of subjects phospholipase A_2 type 1 activity was significantly higher in the secretory phase than in the proliferative phase ($P<0\cdot001$). The median activity (pmol/mg protein/min) for the proliferative phase was 27·6 in normal subjects and 40·4 in women with ovulatory menorrhagia and for the secretory phase the median activity was 144·5 in normal women and 138·1 in women with ovulatory menorrhagia. There was no difference between the two groups of women at either stage of the cycle. Phospholipase A_2 type 2 activity was also higher in the secretory phase than in the proliferative phase ($P<0\cdot05$ for normal subjects and $P<0\cdot001$ for women with menorrhagia). The median activity (pmol/mg protein/min) for the proliferative phase was 94·4 (normal subjects) and 56·6 (women with menorrhagia) and for the secretory phase 148·3 (normal subjects) and 142·5 (women with menorrhagia). The activity of phospholipase A_2 type 2 was significantly lower in the proliferative phase of women with ovulatory menorrhagia compared with normal subjects ($P<0\cdot05$). Phospholipase C activity (nmol/mg protein/min) was significantly higher in women with ovulatory menorrhagia (median 8·2) compared with women with normal blood loss (median 5·5) ($P<0\cdot01$).

Ovulatory dysfunctional uterine bleeding (menorrhagia) remains a common gynaecological complaint for which there is still no ideal medical treatment. Despite the number of women with excessively heavy periods, the aetiology of this distressing condition remains an enigma. The endocrine profiles of women with ovulatory menorrhagia are not different from those with normal menstrual blood loss (Haynes *et al.* 1979). Hence, an imbalance in cycling sex steroids leading to abnormal endometrial growth, as in women with an ovulatory dysfunctional uter-

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ine bleeding, is unlikely to be the explanation. Thus the approach adopted by many workers has been to seek other potential abnormalities of endometrial function. Abnormalities in prostaglandin synthesis have been extensively investigated. Increased prostaglandin synthesis or a relative imbalance in the amount of the vasoconstrictory prostaglandin $F_{2\alpha}$ and the vasodilatory prostaglandin E_2 and I_2 have both been suggested as possible causes of increased menstrual blood loss (Smith *et al.* 1981a; 1981b; Smith *et al* 1982; Rees *et al.* 1984).

We have measured the activity of two isoenzymes of phospholipase A_2 in the endometrium of women with ovulatory menorrhagia and in those with normal menstrual blood loss (Bonney & Franks 1988). Phospholipase A_2 is considered to be the rate limiting enzyme in prostaglandin synthesis since it hydrolyses phospholipids and releases free arachidonic acid, which is then available as substrate for prostaglandin synthesis. Our aim was to determine whether there was an endometrial abnormality in women with ovulatory menorrhagia which altered prostaglandin synthesis at the rate limiting step. However, it was evident that the activity of phospholipase A_2 types 1 and 2 in the endometrium of women with ovulatory menorrhagia was no different from that in women with normal menstrual blood loss.

We also reported (Bonney & Franks 1987) that women with ovulatory menorrhagia had higher endometrial phospholipase C activity than did women with normal menstrual blood loss. Phospholipase C hydrolyses phosphatidylinositol to generate inositol phosphates and diacylglycerol. The action of a second enzyme, diacyglycerol lipase, could potentially release free arachidonic acid as an alternative source of substrate for prostaglandin synthesis. An increase in endometrial phospholipase C activity in women with ovulatory menorrhagia is therefore of relevance to the aetiology of the disorder.

These two studies, however, lacked objective measurements of menstrual blood loss. Since there is substantial evidence to indicate that women do not always make an accurate assessment of their own menstrual blood loss (Fraser *et al.* 1984) we have now included menstrual blood loss measurements in a further study. We report here on the endometrial phospholipase activity (A_2 types 1 and 2 and C) in women with proven ovulatory menorrhagia and in women with normal menstrual blood loss.

Subjects and methods

All women participating in the study were ovulating regularly, as demonstrated by the presence of a secretory endometrium or an ovulatory serum progesterone value. They had no other uterine pathology such as fibroids and had normal ovaries on ultrasound and a normal endocrine profile. None of the patients was using any medication for at least two months before the study. Endometrial tissue was obtained, either by Vabra curettage as an outpatient procedure or by dilatation and curettage under general anaesthesia. A portion of the tissue was sent to the histopathology laboratory for examination by light microscopy and for endometrial dating. The study was approved by the local ethics committee, Parkside Health Authority and all the women gave informed consent.

Subjects with menorrhagia were selected from women with ovulatory cycles who presented with heavy but regular menstrual blood loss. Menstrual blood loss was measured in two cycles for at least 2 months after curettage, using the alkaline haematin method, as described by Hallberg & Nillson (1964). An average monthly blood loss in excess of 80 ml was classified as menorrhagia.

Women in the control group were recruited from those who presented for clip sterilization or infertility due to tubal defects. Women who complained of menorrhagia but were found subsequently to have normal periods (blood loss of <40 ml in this study) were also included in this group.

Endometrial tissue was frozen on dry ice immediately after collection and stored at −70°C. Before the assay, the tissue was homogenized using a polytron homogenizer (Kinematica GmbH, Lucerne, Switzerland) at a concentration of 80–100 mg tissue per ml in 0·25 M sucrose and centrifuged at 250 *g* for 5 min. The supernatant was decanted and retained for phospholipase assay. The protein concentration of the supernatant was measured by the method of Lowry *et al.* (1951).

Assay of phospholipase activity

Phospholipase A_2 activity (types 1 and 2) was measured as described previously (Bonney & Franks, 1987; 1988). In the present study the substrate used was 1-stearoyl 2[^{14}C]-arachidonyl phosphatidylcholine (Amersham International plc, Bucks, UK) and the incubation mixture contained [^{3}H]-arachidonic acid to monitor procedural losses.

Phospholipase C activity was measured by incubating a tissue extract with the radiolabelled substrate, 3 - phosphatidyl - [2 - ^{3}H] - inositol (Amersham International). The [^{3}H] hydrolysis products (free inositol and inositol phosphates) were measured, as an index of enzyme activity. The assay method is described in detail in a previous publication (Bonney & Franks 1987).

Data were assigned to the proliferative or secretory phase of the cycle according to histological dating of the tissue. The timing of the last menstrual period and serum progesterone values were also taken into account when making the assessment. Since the data were not normally distributed, they were analysed by Mann Whitney *U* test.

Results

Phospholipase A_2 type 1 activity

The activity of phospholipase A_2 type 1 in proliferative and secretory phase endometrium from women with and without proven menorrhagia are presented in Fig. 1. In both groups phospholipase A_2 type 1 activity was significantly higher in the secretory phase than in the proliferative phase ($P<0{\cdot}001$) but there were no differences at either stage of the cycle between the two groups. These findings accord with our previous studies both with respect to the cyclical differences in phospholipase A_2 activity (Bonney 1985; Bonney *et al.* 1987; Bonney & Franks 1988) and to the absence of altered activity in the presence of ovulatory menorrhagia (Bonney & Franks 1988).

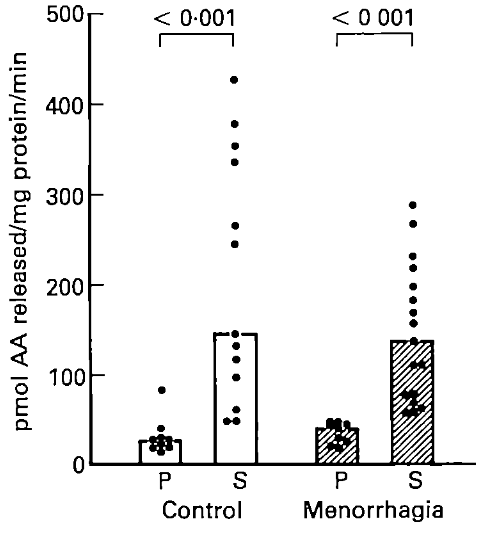

Fig. 1. Phospholipase A_2 type 1 activity, expressed as pmol arachidonic acid (AA) released/mg protein/min, in the endometrium from control subjects (open bars) and from women with proven ovulatory menorrhagia (hatched bars) obtained in the proliferative (P) or secretory (S) phase of the cycle. Each point represents an individual observation (each an average of duplicate estimations) and the vertical bar represents the median. Proliferative versus secretory phase for both groups: $P<0{\cdot}001$ (Mann Whitney *U* test).

Phospholipase A_2 type 2 activity

Figure 2 illustrates the data obtained for phospholipase A_2 type 2 activity in the endometrium of women with and without proven menorrhagia. There was a significant difference in enzyme activity between the proliferative phase and secretory phase of the cycle in both groups of women. There was a small although significant increase in enzyme activity in the secretory phase tissue from women in the control group

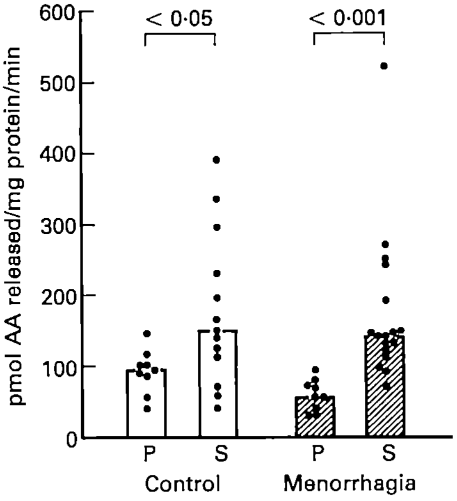

Fig. 2. Phospholipase A_2 type 2 activity, expressed as pmol arachidonic acid (AA) released/mg protein/min, in the endometrium from control subjects (open bars) and from women with proven ovulatory menorrhagia (hatched bars) obtained in the proliferative (P) or secretory (S) phase of the cycle. Each point represents an individual observation (each an average of duplicate estimations) and the vertical bar represents the median. Phospholipase A_2 type 2 activity is expressed as pmol arachidonic acid (AA) released per mg protein per min Proliferative *vs* secretory phase: control group, $P<0{\cdot}05$; menorrhagia group, $P<0{\cdot}001$ Control group versus menorrhagia group: proliferative phase $P<0{\cdot}05$ (Mann Whitney *U* test.

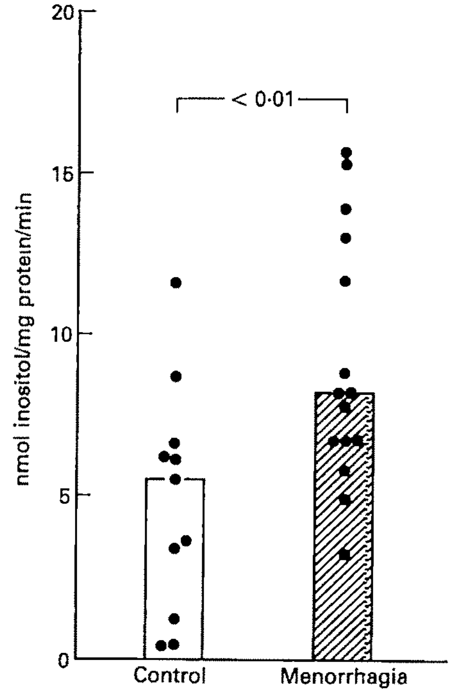

Fig. 3. Phospholipase C activity in the endometrium from control subjects (open bar) and from women with proven ovulatory menorrhagia (hatched bar) Each point represents an individual observation (each an average of duplicate estimations) and the vertical bar represents the median. Phospholipase C activity is expressed as nmol water soluble products (inositol, inositol phosphates) produced per mg protein per min. Control group versus menorrhagia group: $P<0{\cdot}01$. (Mann Whitney *U* test).

($P<0{\cdot}05$) but a highly significant increase in the secretory phase in women with ovulatory menorrhagia ($P<0{\cdot}001$). The difference in activity between the two phases of the cycle was more apparent in women with menorrhagia because in this group, phospholipase A_2 type 2 activity was significantly lower in the proliferative phase compared with the control group ($P<0{\cdot}05$) but secretory phase activity was no different between the two groups of subjects. In our earlier study (Bonney & Franks 1988) and in a more recent study (Bonney *et al.* 1990a) there was a trend towards a similar finding but the difference was not statistically significant.

Phospholipase C activity

Since there was no difference between proliferative and secretory phases of the cycle with respect to endometrial phospholipase C activity both in the present study and in an earlier study (Bonney & Franks 1987), the data were pooled within each group. In agreement with our previous findings there was a significant increase in endometrial phospholipase C activity in the group with ovulatory menorrhagia ($P<0{\cdot}01$) (Fig. 3).

Discussion

Prostaglandins are considered to play a key role in the mechanism of menstruation (Pickles *et al.* 1965; Wiquist *et al.* 1971; Anderson *et al.* 1976; Guillebaud *et al.* 1978) and are increased in the endometrium and menstrual fluid of women suffering from menorrhagia (Pickles *et al.* 1965; Rees *et al.* 1984). Since the rate limiting factor in the synthesis of prostaglandins is a supply of free arachidonic acid, one way in which prostaglandin synthesis may be regulated is by modulating the activity of phospholipases. The hypothesis governing our earlier investigations was that the activity of either phospholipase A_2 or phospholipase C or both may be increased in women with ovulatory menorrhagia. Phospholipase A_2 type 1 is a membrane bound enzyme which is calcium dependent and is maximally active at pH 7·5–9·0. It is located in the glandular component of the endometrium and accordingly it increases four-fold in activity during the secretory phase of the menstrual cycle. Activity reaches a maximum in the early to mid secretory phase (Bonney 1985; Bonney & Franks 1987). A second isoenzyme (phospholipase A_2 type 2) occurs the endometrial stromal tissue (Bonney & Franks 1987) and is also present in the myometrium (Bonney & Wong 1988). It differs from type 1 in that it is a calcium independent enzyme with an optimum pH of 6·5–7·0 and is unstable after freezing and thawing. These characteristics are indicative of cytosolic phospholipases (Vadas & Pruzanski 1986) and suggest that phospholipase A_2 type 2 may be a cytosolic enzyme but this has yet to be proved. The activation of either of these isoenzymes may be necessary for the generation of arachidonic acid for prostaglandin synthesis but in neither case is there a marked increase in enzyme activity at menstruation.

In our previous study (Bonney & Franks 1988), we found no difference in the endometrial activity of either type 1 or type 2 phospholipase A_2 at either stage of the menstrual cycle between women complaining of ovulatory menorrhagia and those with normal menstrual blood loss. The assessment of blood loss was not objective although haemoglobin concentrations were taken into account. The present study includes objective menstrual blood loss measuremens and the findings of the two studies are essentially the same. An identical profile of phospholipase A_2 type 1 activity was found in the two groups; both groups showed an approximate four-fold increase in activity during the secretory phase. However, the pattern of phospholipase type 2 activity in the present study differed from that of our earlier study in that there was a small but significant increase in activity in the secretory phase of the cycle. The difference was more marked in the women with menorrhagia because these women had significantly lower phospholipase A_2 type 2 activity in the proliferative phase than the control women. There was a suggestion of such a difference in our earlier study but it was not statistically significant. In women with polycystic ovaries the activity of phospholipase A_2 type 2 is markedly increased in proliferative phase endometrium compared with women with normal ovaries (Bonney *et al.* 1990a). The cause of the increase is not known but since women with polycystic ovaries have a thicker endometrium than women with normal ovaries (Adams *et al.* 1987), we have suggested that the increased enzyme activity may be a marker of abnormal endometrial development and function. In women with ovulatory menorrhagia there is no evidence of a morphological abnormality of the endometrium. However, there may be a biochemical abnormality in the endometrium during the proliferative phase as evidenced by the lower endometrial phospholipase A_2 activity in these women. It is possible that these women have a defect in endometrial regeneration and repair during the early proliferative phase which gives rise to menstrual irregularities later in the cycle. Growth factors such as epidermal growth factor (EGF) or transforming growth factor α (TGFα) may be implicated in regeneration and repair of the endometrium since these factors regulate endometrial stromal cell proliferation *in vitro* (Bonney *et al.* 1990b). Growth factors also stimulate arachidonic acid release and prostaglandin synthesis by uterine tissues (Mitchell 1987; 1988) and arachidonic acid release by endometrial glands *in vitro* (Beesley *et al.* 1989) and therefore may also be more directly involved in menstruation.

Whether phospholipase A_2 plays a key role in regulating prostaglandin synthesis at the time of menstruation remains speculative. There is certainly no evidence of a sharp increase in the activity of either isoenzyme immediately before the onset of bleeding but other factors must be taken into account. Measurements of enzyme activity *in vitro* may not be relevant to the situation *in vivo* where an enzyme activation mechanism, unassociated with an increase in enzyme synthesis, may be operating. This is likely to be the case with enzymes such as membrane bound phospholipases which act in close proximity to their substrate. Furthermore, the levels of arachidonic acid in the tissue may be adequate without phospholipase activation and it may be the prostaglandin synthetase complex which regulates prostaglandin synthesis. Other enzymes, namely prostaglandin ketoreductases and dehydrogenases, may also contribute to determining the final balance of prostaglandins present at a given time.

The present study is supportive of our earlier work in which we demonstrated that there was an increase in the activity of phospholipase C in the endometrium of women with ovulatory menorrhagia (Bonney & Franks 1987). It is important to note, however, that activation of phospholipase C generates diacylglycerol which may then be metabolized either to arachidonic acid by mono- and diacylglycerol lipases or to phosphatidic acid via diacylglycerol kinase. Therefore, a direct relation between phospholipase C activity and prostaglandin production cannot be assumed. Nevertheless the role of phospholipase C is of interest and requires further investigation.

Triglycerides may also contribute arachidonic acid for prostaglandin synthesis. A role for triglycerides in the generation of arachidonic acid for prostaglandin synthesis has been demonstrated in the kidney (Liston & Nasjletti 1987) and in bovine endothelial cells (Denning *et al.* 1983) and it is evident from our own studies that triglycerides contribute to the pool of free arachidonic acid in human endometrium (Bonney *et al.* 1990c) particularly in the stromal cells (Beesley *et al.* 1990; 1991). If this is the case, should we perhaps be looking at the role of triglyceride lipases in the regulation of menstruation?

Acknowledgments

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Controlling Rh haemolytic disease of the newborn in India

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Summary. The question whether India should institute a national programme of Rh screening and postpartum Rh immune globulin prophylaxis needs to be addressed, especially because of the recent emphasis on primary maternal and child health care. Given the absence of relevant community based data, decision analysis techniques were used to address these issues. The results reveal that the estimated cost per case of Rh HDN prevented through postpartum immune globulin prophylaxis is lower than the cost per case of Rh HDN treated through a curative strategy. However, the financial and infrastructural requirements of the preventive programme mean that such prevention may not be feasible at present. With the achievement of the Indian Government's stated objectives of population control, however, disease incidence should fall by 30% from 5·90/1000 births in 1981 to 4·13/1000 births by the year 2000, even in the absence of a prophylaxis programme.

Should India institute a national programme for controlling Rh haemolytic disease of the newborn (Rh HDN)? This question needs to be asked especially because of the increasing emphasis being accorded to primary maternal and child health care in recent years. Further, the prevailing dichotomy that exists in obstetric practice between rural and urban areas (with most private doctors in urban areas routinely offering such a facility) needs to be resolved or at least justified. Finally, even if a programme of Rh screening and postpartum immune globulin (Ig) prophylaxis were to prove financially impossible at present, the perspective for the future needs to be clarified.

Such a discussion must necessarily examine a related issue arising from the fact that the reported dramatic decline in the incidence of Rh HDN in many countries is a consequence of two factors: the widespread postpartum use of Rh Ig and a decline in fertility (Knox 1976; Adams *et al.,* 1981). Since India differs from these countries with respect to resources, fertility trends and the prevalence of the Rh negative phenotype, the relative merits of these two modes of prevention need to be critically appraised. In the absence of population based data to answer these questions, we have used decision analysis techniques to assess the likely impact of each of the strategies of disease control.

Methods

Analytical model

Decision analysis permits a comparison of alternative strategies (Grundy & Reinke 1973) Using this technique, we analyzed the hypothetical experience of various cohorts of Indian women, through their reproductive lifespan. Variables incorporated in the model included prevalence of the maternal Rh type, prevalence of the paternal Rh genotype, protection afforded by ABO blood group incompatibility

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against Rh sensitization, probability of parity progression, probability of miscarriage and induced abortion, probability of Rh maternal sensitization and probability of disease, given maternal sensitization (shown in Figs. 1, 2). The probabilities assigned to the branches at the various chance nodes were based on published data; Western figures were used for biological variables (e.g. probability of maternal sensitization) and national statistics were used wherever indicated (e.g. probability of parity progression).

The incidence of Rh haemolytic disease of the newborn was calculated for different cohorts of women by repeating the iteration using appropriate data. For instance, the incidence for the cohort of women aged 15–44 years in 1981 was determined using the parity progression ratio specific to that group of women. The iterative process was repeated for the cohort of women aged 50 years and above in 1981, and also for the cohort of women aged 15 to 44 years in the year 2000, under different assumptions of fertility (specified below). Similarly the reduction in Rh HDN incidence brought about by postpartum Ig prophylaxis was also calculated for the various cohorts. The cost per case averted through screening and prophylaxis was estimated from the component costs of such a programme (specified below). Similarly the cost incurred in the absence of Ig prophylaxis, i.e. the cost of a curative approach, was also determined. The annual cost of each programme was estimated from the cost per case averted/treated and the estimated crude birth rate of the year in question.

Estimation of disease incidence in the absence of Rh Ig prophylaxis

Number of married women of reproductive age (decision node 1). The numbers of married women of reproductive age for the years 1981 and 2000 were taken to be 119 974 000 and 190 943 000 respectively (Ross *et al.*, 1988).

Probability of the Rh negative type among women (chance node 2). A probability of 0·05 was assigned for this, based on prevalence rates observed in the Indian population (Bhakoo

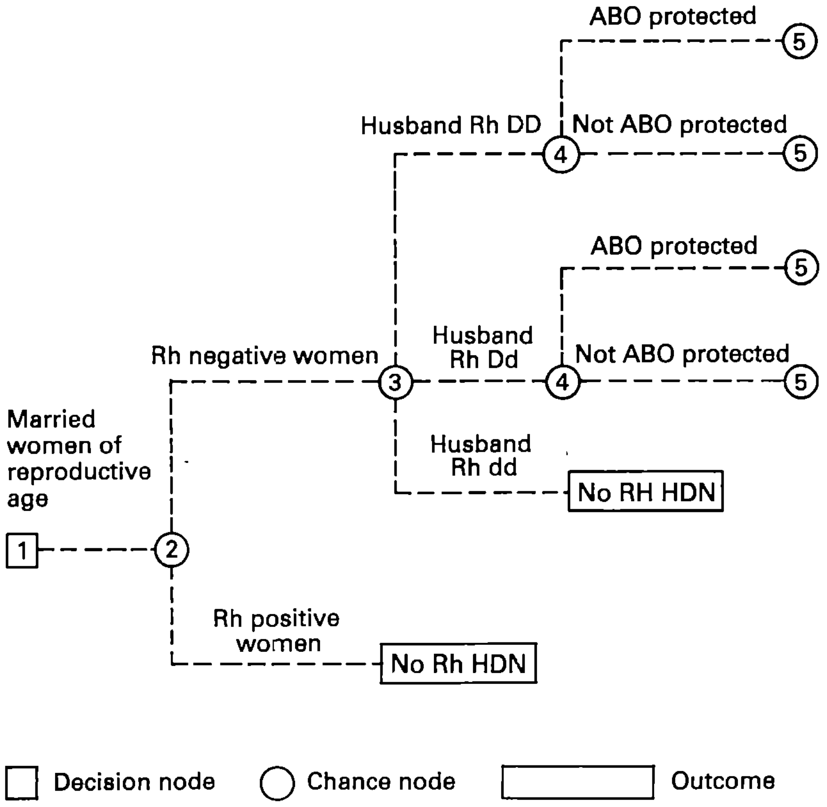

Fig. 1. Decision tree for estimating the incidence of Rh haemolytic disease of the newborn in India based on the blood group factors of married women and their husbands.

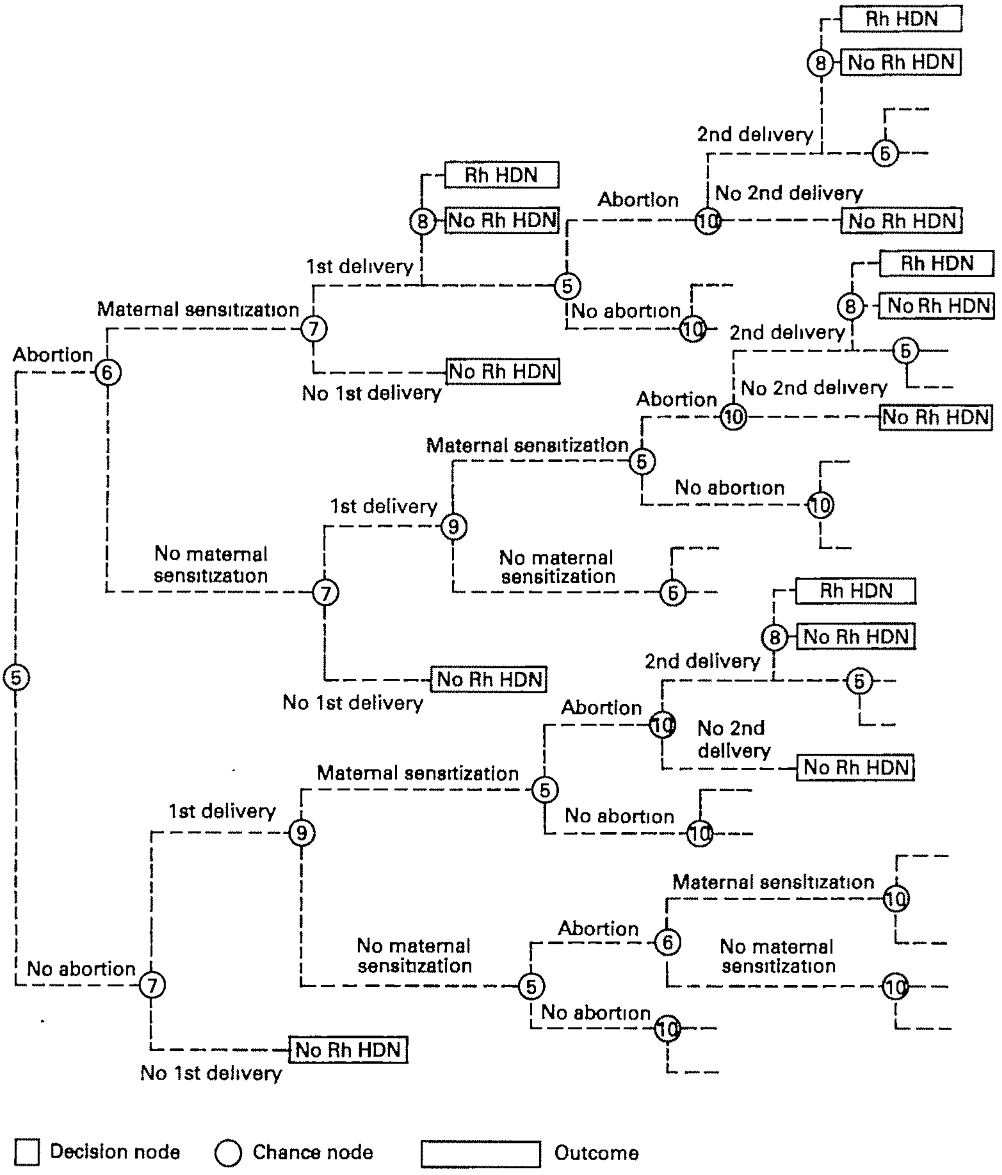

Fig. 2. Decision tree for estimating the incidence of Rh haemolytic disease of the newborn in India (continued from Fig 1) based on Rh negative women and with Rh positive husbands (note abortion includes induced abortion and miscarriage).

1982; Mudaliar & Krishnamenon 1984; Masani & Parikh 1986).

Probability of the husband's Rh genotype being dd/Dd/DD (chance node 3). Husbands were classified according to the clinically relevant Rh (D) antigen into those homozygous for the Rh positive trait (DD), heterozygous for the Rh positive trait (Dd) and those homozygous for the Rh negative trait (dd). The frequency of the genotype dd was taken to be 0·05 and using the Hardy Weinberg law (Gorman 1975) the frequency of the genotypes Dd and DD were estimated to be 0·347 and 0·603 respectively.

Probability of ABO protection (chance node 4). The probability of ABO incompatibility in the Indian population was estimated to be 0·14 The distribution of ABO blood groups in India is: Group A, 23·5%, Group B 34·5%, Group O 34·5% and Group AB 7·5% (Hurkat & Mathur 1972). From these data, gene frequencies and genotype frequencies were calculated and the probability of a group O woman having an ABO incompatible pregnancy was determined assuming random mating.

Probability of parity progression (chance nodes 7, 10, 11 . . . 18 i.e. up to parity 10). The parity progression ratio (the probability that a woman of parity p_x will attain a parity of p_{x+1}) for Indian women aged 15 to 44 years, and for those aged 50 years and above, was taken from the 1981 all-India census data (Census of India 1981; Registrar General 1983). Since this demographic index does not include stillbirths (which can cause maternal sensitization and which may be a consequence of Rh HDN), a correction factor was applied to each value. A stillbirth rate of 10·6/1000 births was used to make the correction for women aged 15 to 44 years in 1981 (Sample Registration System, 1981). For the generation of women aged 50 years and above in 1981, the stillbirth rate used for correction was 15/1000 births whilst the projected stillbirth rate for the year 2000 was assumed to be 8/1000 births. The predicted fertility for the cohort of the year 2000 was assumed to follow one of three possible patterns. Thus, parity progression under the first assumption was the same as that of the 1981 cohort aged 15–44 years, except for the additional condition that no woman would exceed parity four. Similarly for assumption 2, it was stipulated that no woman would exceed parity three and finally, under the third assumption, that no woman would exceed parity two. Under the first assumption, the completed family size would be 2·4, whilst under assumptions 2 and 3 the completed family size would be 2·0 and 1·5 respectively (stillbirths excluded). The first assumption was built around the Government of India's stated objective of achieving a net reproduction rate of 1 by the year 2000; the corresponding family size for achieving such an objective being 2·3 (Government of India 1981). The other two scenarios represent more extreme positions, comparable to the fertility patterns in some Western countries.

Probability of miscarriage and abortion (chance node 5). The rate of miscarriage in India was taken to be 5/1000 population per year (Shah Committee Report 1982a). This figure translates to 10 miscarriages/100 births. The rate of abortion was more difficult to estimate as Health Ministry figures are thought to represent only a fraction of the total. Moreover, these figures include pregnancies where abortion is combined with sterilization. Such cases are not relevant to the calculation at issue since Rh (D) alloimmunization in sterilized women would not result in disease occurrence. Nevertheless, approximations for the relevant rates were made and sensitivity analyses were undertaken to assess the effect of varying the assumptions. Estimates from the mid-1960s indicate a rate of abortion of 15/100 births (Shah Committee Report 1971). This rate was applied to the cohort of women aged 50 years and above in 1981. For the cohort aged 15–44 years in 1981 and the three cohorts of the year 2000, the rate of abortion was assumed to be 25/100 births and 35/100 births, respectively.

Probability of maternal sensitization (chance nodes 6 and 9). The probability of maternal sensitization following a Rh positive delivery in the absence of postpartum Rh Ig administration was assumed to be 0·1 for ABO protected pregnancies and 0·17 when no protection due to ABO incompatibility was present (Ascari *et al.*, 1969). The probability of maternal sensitization after the miscarriage of a Rh positive fetus was taken to be 0·02 and that after an abortion 0·045 (Bowman 1985). The probability of a Rh negative woman conceiving a Rh positive fetus when the husband's Rh genotype was DD was assumed to be 1, while the same probability when the husband's genotype was Dd was assumed to be 0·5.

Probability of Rh haemolytic disease of the newborn after maternal sensitization (chance node 8). This was assigned a value of 0·6 and included mild, moderate and severe cases of Rh haemolytic disease of the newborn (Adams *et al.*, 1984).

Estimation of disease incidence given a programme of Rh Ig prophylaxis postpartum

Rh Ig was administered to all unsensitized Rh negative women with Rh positive husbands who gave birth to a Rh positive baby or who had an abortion. The efficacy of postpartum Rh Ig in preventing maternal sensitization was assumed to be 0·95 (Lim *et al*, 1982).

Costing the preventive and treatment options

All costs were estimated at current prices, thus enabling comparisons across cohorts. The cost of treatment was estimated as the cost of health care services required, in addition to standard obstetric procedures and neonatal care, in cases of Rh (D) alloimmunization.

Cost of the preventive option (Rh Ig prophylaxis)

The recurring cost of this programme was calculated based on a cost of Rs 25 (£1) per Rh typing test, Rs 375 (£15) per 300 μg dose of Rh Ig, Rs 150 (£6) per 100 μg dose of Rh immune globulin, and Rs 37 (£1·5) for the indirect Coombs test.

Under the model it was assumed that Rh typing was done once for all married women of reproductive age who had one child. Rh typing was also done for the husbands of all Rh negative women who had one child and also for all babies born to Rh negative women with Rh positive husbands. It was assumed that Rh Ig was administered to all unsensitized Rh negative women with Rh positive husbands who gave birth to an Rh positive baby (300 μg) or who had had an abortion (100 μg). Finally it was assumed that and indirect Coombs test was done antenatally on all Rh negative women (with Rh positive husbands) at risk, i.e. those who had given birth to a Rh positive baby in the immediately preceding pregnancy or those who had an abortion immediately before the pregnancy. The cost per case averted was estimated by dividing the cost of the programme by the number of cases averted as a consequence of prophylaxis.

Cost of the treatment option (no Rh Ig prophylaxis)

The cost of this option was estimated based on a cost of Rs 400 (£16) per amniocentesis, Rs 750 (£30) per intrauterine blood transfusion, Rs 750 (£30) for a normal, tertiary hospital delivery, Rs 1000 (£40) for induction of labour and delivery at 37 weeks, Rs 1500 (£60) for delivery by caesarean section, Rs 1000 (£40) for the neonatal care of a mildly affected infant, Rs 2500 (£100) for the care of a moderately affected infant and Rs 5000 (£200) for the care of a severely affected infant.

The plan of management followed was a standard one (Crosby & Block 1987) and was chosen after consideration of the technology available and likely to be available in the country. The model assumed that all married women attaining parity 1 were typed along with their husbands, and that an indirect Coombs test would be performed on all women at risk (defined above). Women found to be sensitized would be subjected to repeat indirect Coombs tests a further four times, on average. Amniocentesis would be undertaken at 28 weeks based on the result of the serial indirect Coombs titres. It was assumed that 5% of sensitized pregnant women with an Rh negative fetuses would have an anamnestic rise in Coombs titres and would require monthly amniocentesis (an average of three times through the pregnancy). It was further assumed that 60% of sensitized women with unaffected Rh positive fetuses would have an amniocentesis every month (an average of three times); amniocentesis would not be done for the other 40% since the serial indirect Coombs titres would show them to be not at risk (Kelsall *et al.*, 1958). Mildly affected pregnancies would have the procedure done monthly (an average of three times) with labour induced at 37 weeks. Moderately affected pregnancies would be subjected to amniocentesis every 2 weeks (an average of four times) and delivery would be effected by caesarean section at 34–36 weeks. Amniocentesis would be done weekly on severely affected pregnancies (an average of six times) with delivery at 32–34 weeks by caesarean section. One intrauterine blood transfusion was assumed for all severely affected fetuses on average, and for half of those moderately affected.

The cost per pregnancy treated was obtained by dividing the total cost of this option by the number treated successfully, assuming that 10% of all severely affected fetuses succumbed in spite of treatment

Sensitivity analyses

Sensitivity analyses were performed using 10% as the proportion protected by ABO incompatibility as against 14% used to obtain the point estimate. This was done to assess the effect of assortative mating producing a lower level of ABO incompatibility, the assumption under the point estimate being that mating was random. Sensitivity analyses were also done to assess the effect of varying the rates of abortion. For the generation of women aged 50 years and above in 1981, the lower bound of this rate was kept at 10 abortions/100 births and the upper bound at 20. For the generation of women aged 15–44 in 1981, the lower and upper bounds were altered to 20 and 30 abortions/100 births, while for the cohort of the year 2000 the relevant figures were taken to be 30 and 40 abortions/100 births.

Results

The results show that the incidence of Rh HDN has fallen by 20% between the two generations considered for 1981, entirely as a consequence of a decline in fertility. Continued reductions in fertility would result in a further significant decline in disease occurrence; the first assumption for the year 2000 showed a 30% decrease in comparison to the younger 1981 cohort. Rh Ig prophylaxis dramatically reduced the incidence, even in the absence of a check in the fertility pattern (Table 1).

Altering the assumptions for the two variables considered in the sensitivity analyses did not make a substantive difference to the point estimate. Reducing the proportion of the population protected by ABO incompatibility altered the incidence of Rh HDN from 5·90/1000 births (1981) to 5·98/1000 births—an increase of 1·4%. Similarly, the sensitivity analyses for abortion produced only a negligible change in the point estimate for disease incidence. The 1981 cohort aged 15–44 years showed a 1% difference while the maximum effect was noted for the cohort of the year 2000 (assumption 3) which showed a 2·6% difference from the point estimate.

The cost per case averted through Ig prophylaxis and the cost per case treated for the various cohorts are presented in Table 2. The preventive option of postpartum prophylaxis was found to be about 1·8 times less expensive than the treatment option for the 1981 cohort aged 15 to 44 years, and 1·3 times less expensive for the cohort of the year 2000 under assumption 1. The recurring annual cost of the prophylaxis programme was found to be Rs 603·7 million (£24·2 million) in 1981 and Rs 599·4 million (£24 million) for the year 2000 under assumption 1. The corresponding annual cost of the treatment programme was found to be Rs 1123 million (£44·9 million) and Rs 799·3 million (£32 million) respectively. It was estimated that 7·4 million Rh typing tests were required annually in 1981 and 8·3 million in the year 2000 under assumption 1. A total of 785 000 indirect Coombs tests were required annually in 1981 and 704 000 tests in the year 2000. The programme used 877 000 doses of 300 μg Ig and 381 000 doses of 100 μg Ig annually in 1981, whereas Ig requirement for the year 2000 (assumption 1) was 803 000 doses of 300 μg Ig and 443 000 doses of 100 μg Ig per year. Each primary health centre providing services for a population of 100 000 people performed 1074 Rh typing tests and 115 indirect Coombs tests in 1981. Under assumption 1, in the year 2000, the relevant figures would be 830 Rh typing tests and 70 indirect Coombs tests respectively. The number of Ig doses administered by each primary health centre was estimated to be 125/year in the year 2000 under assumption 1.

Table 1. Estimated incidence of Rh haemolytic disease of the newborn (HDN) among various cohorts with and without a postpartum immune globulin prophylaxis programme

Cohort	Rate of Rh HDN/1000 births	
	No prophylaxis	Prophylaxis
1981		
Generation >50 years	7·50	0·49
Generation 15–44 years	5·90	0·37
2000		
Assumption 1	4·13	0·23
Assumption 2	3 16	0·17
Assumption 3	1·90	0·10

Figure 3 shows the cumulative probability of maternal Rh sensitization, according to the order of delivery, for a Rh negative woman with a Rh positive husband in populations with a Rh negative rate of 5% (i.e. India) and 15%. This risk of sensitization was seen to be higher with each succeeding delivery for Indian women. The finding is not unexpected since the probability that the woman in question will have a Rh positive homozygous husband is higher in the population with the lower prevalence (Adams *et al.*, 1981). This implies that there is a relatively greater indication for Ig prophylaxis for a Rh negative woman in the Indian population than in one from a population with a higher prevalence of the Rh negative phenotype.

Figure 4 shows the rates of Rh HDN incidence for populations with varying rates of Rh negative prevalence, assuming the fertility level of the 1981 cohort. As expected, disease incidence increases with increasing prevalence of the Rh negative phenotype. Further, it appears that a population with a high prevalence of the Rh negative phenotype will achieve a greater impact through prophylaxis, in comparison with a population with a relatively low prevalence. This is reflected in the cost per case averted. For instance, altering the Rh negative prevalence for

Table 2. Comparison of the cost per case averted by a programme of Rh immune globulin prophylaxis and cost per case treated for various cohorts

Cohort	Cost per case averted		Cost per case treated	
	Rupees	Pounds	Rupees	Pounds
1981, generation 15-44 years	4 700	188	8 475	339
2000				
Assumption 1	7 350	294	9 575	383
Assumption 2	10 150	406	10 900	436
Assumption 3	18 950	758	15 450	618

the cohort of the year 2000 under assumption 1 to 15% (other variables being held constant), led to a cost per case averted of Rs 6900 (£276) in comparison to a cost of Rs 7350 (£294) when the Rh negative prevalence was kept at 5%.

Discussion

The postpartum prophylaxis to treatment ratio of 1·8 obtained for the 1981 cohort aged 15 to 44 years, and 1·3 for the cohort of the year 2000 under assumption 1, compares with a ratio of 2·7 obtained elsewhere (Baskett & Parsons 1990). These ratios are not comparable, however, because of differences in study methods and treatment strategy. For instance, the Canadian study included office administration fees and programme staff salaries in the cost of the prevention option. These costs were not included in the present study because it was anticipated that the increased work load (125 injections/100 000 population per year) could be easily incorporated within present staffing or, at most, with a minimal cost increase. On the other hand, the cost of Rh typing and indirect Coombs tests (the latter required to determine prophylaxis failures for whom Ig would not be subsequently indicated) were included in this study but apparently not in the Canadian one. Thirdly, the efficacy of postpartum prophylaxis was found to be 88% in the Canadian study, whereas our study assumed an efficacy rate of 95%. The critical difference, however, arose as a result of the treatment strategy assumed. In the Canadian study, expensive neonatal intensive care accounted for high treatment expenses whereas our study considered such a sophisticated treatment modality inappropriate for a third world country.

Obviously, cost effectiveness estimates for Rh disease are location-specific and depend mainly on treatment strategy and population fertility and also on the prevalence of the Rh negative phenotype. It should be noted further, that had economic losses to society (indirect non-medical costs incurred by the patient) been included in the cost of the curative option, the cost-effectiveness ratios would have tilted further in favour of the preventive measure in both studies.

Even though Ig prophylaxis appears to be the

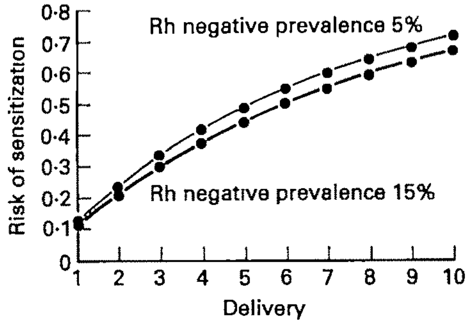

Fig. 3. Cumulative risk of maternal Rh sensitization according to birth order for a Rh negative woman with a Rh positive husband in populations with a Rh negative prevalence of 5% and 15%.

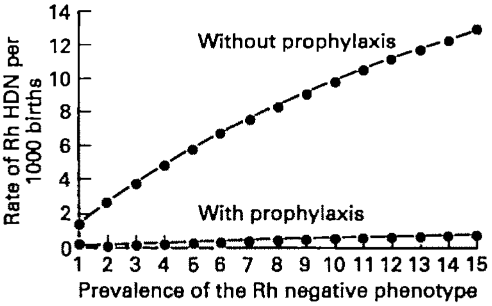

Fig. 4. Rate of Rh haemolytic disease of the newborn per 1000 births according to rate of Rh negative prevalence, assuming the fertility level of the 1981 cohort aged 15-44 years

financially favourable alternative, the high recurring costs of the programme would not permit its ready implementation in India. A developing country with resource constraints and many unmet health needs must necessarily allocate priorities for expenditure on health services based on careful cost-benefit analyses. Such studies are difficult to execute, so a clear definition of priorities is difficult. Nevertheless, it appears that with the introduction of reliable and inexpensive tests like the 'rapid plasma reagin test', for example, antenatal detection and treatment of syphilis may deserve precedence over Rh screening and prophylaxis. Estimates made using techniques identical to those used in the present study show that the cost per case of congenital syphilis averted would work out to be far lower than the cost per case of Rh HDN averted, even if a low estimate of 0·5% for syphilis prevalence is used.

Other problems in initiating a screening and prophylaxis programme arise because of infrastructural constraints. Primary health centres do not as yet possess the infrastructure to perform Rh typing and indirect Coombs tests. Also medical record keeping, a poorly developed discipline in India, would need to be much upgraded. Finally, the large volumes of Rh Ig required would call for a huge increase in the indigenous production capacity.

The phenomenon illustrated in Figs. 3 and 4, lies at the heart of the Indian dilemma. Whereas the low prevalence of the Rh negative phenotype ensures a relatively higher degree of risk for the Rh negative Indian woman, it also results in a greater cost for screening and prophylaxis per case averted. This, coupled with the impoverished state of the economy, means that neither the individual nor the government is in a position to meet the entire cost of controlling the disease. A possible first step towards solving this problem could be for the government to introduce a compulsory Rh typing service as part of its antenatal care programme. Women found to be Rh negative could be advised about prophylaxis etc., to be undertaken at their own expense. While such a policy would inevitably invite criticism on various grounds, it is worth noting that under the existing system the only reason why the question of Ig prophylaxis does not arise is because Rh status is largely unknown.

Providentially for the Indian population, the low prevalence of the Rh negative phenotype has led to a relatively low incidence of Rh HDN, even in the absence of postpartum Ig administration. While financial realities may not permit the initiation of a government funded programme of prophylaxis, the prospect of a 30% reduction in disease incidence, over the next decade, offers an added incentive for reducing fertility through better education and health service availability.

Acknowledgment

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Fetal umbilical artery velocity waveforms and subsequent neonatal outcome

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Summary. Flow velocity waveforms (FVWs) from the fetal umbilical artery were recorded from 2178 pregnant women over a 6-year period. All of them had an obstetric factor indicating increased risk of fetal compromise. A total of 6749 studies was recorded. The systolic diastolic (AB) ratio was measured and classified as normal (<95th centile), elevated (95–99th centile), high (>99th centile) or extreme (absent diastolic flow). The results of these studies have been related to subsequent fetal and neonatal outcome. An abnormal umbilical artery FVW was associated with shorter gestation and infants with lower birthweight, shorter length and lower ponderal index. There was a highly significant association between an abnormal FVW and the birth of an infant small for gestational age. The significance of the association increased with the increased abnormality of the umbilical artery FVW and this was independent of gestational age. Preterm infants associated with high or extreme AB ratios spent twice as long in the neonatal nursery than those with normal AB ratios. Analysis of 794 pregnancies studies serially indicated that an abnormal FVW in which the AB ratio was increasing, in contrast to a decreasing AB ratio, predicted a poor outcome for both size at birth and duration of neonatal intensive care. We conclude that in high risk pregnancy Doppler umbilical artery FVW studies predict the most compromised fetuses in terms of growth retardation and requirements for neonatal intensive care.

For an investigative method to be accepted as a clinically useful test of fetal welfare on which action and intervention may be based, it is necessary to know the adverse outcomes predicted by an abnormal result. The place of Doppler studies in obstetric practice has received much attention. The fetal umbilical artery flow velocity waveform (FVW) has been shown to detect a vascular pathology in the placenta (Giles *et al.* 1985). It has been suggested that fetal compromise follows this placental lesion (Trudinger *et al.* 1985a). Almost all clinical studies have reported the value of fetal umbilical artery FVWs in identifying small-for-gestational age (SGA) fetuses in pregnancies complicated by a fetal risk factor (Schulman *et al.* 1984; Erskine & Ritchie 1985; Reuwer et al. 1984; Trud-

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inger *et al.* 1985b). All of these studies have been relatively small with fewer than 60 pregnancies having an abnormal fetal outcome. Furthermore, as not all SGA fetuses are compromised, tests are required to identify those fetuses at risk of death *in utero*, distress in labour, neonatal problems, and handicap. Umbilical artery FVWs can identify the small fetus that is at risk of perinatal asphyxia (Trudinger *et al.* 1985b; Laurin *et al.* 1987, Rochelson *et al.* 1987a; Berkowitz *et al.* 1988b). In the sequence of events associated with deteriorating fetal condition, failure of ultrasound growth (Berkowitz *et al.* 1988a) and changes in non-stressed fetal heart rate monitoring (Trudinger *et al.* 1986) occur after the abnormal FVW is identified. Analysis of blood gases in samples obtained by cordocentesis indicate that some, but not all, extremely abnormal FVWs are associated with fetal hypoxaemia (Nicolaides *et al.* 1988), but such studies are not suitable for wide scale application. As important as predictions of size or condition of the fetus are measures of neonatal morbidity and mortality. This is a very important consideration in making obstetric decisions. The aim of the present study was to determine both the fetal and neonatal outcome correlates. By reporting a very large group of pregnancies at one centre, correlations between the degree of abnormality in the FVW and outcome, with the necessary correction for gestational age, are possible.

Subjects and methods

During the 6-year period between 1983 and 1988 a total of 2178 women, with a singleton pregnancy delivered after 26 weeks gestation, was examined on 6749 occasions. Three or more studies were performed in 794 women. The indications for examination are listed in Table 1. Suspected fetal compromise included decreased fetal movements, SGA fetuses and abnormal fetal welfare test. The gestational age at examination ranged from 12·1 weeks (first study) to 43·6 weeks (last study). The mean gestational age at delivery was 37·7 weeks (SD 3·2, range 26–43·6). The mean last study to delivery interval was 12·5 days (SD 16·5) and in 68% of the women the last study was made within 10 days of delivery (mode 1 day). The mean maternal age was 27·4 years (SD 5·2); 897 women were nulliparous and 1281 were multiparous.

The umbilical artery FVW was recorded using Doppler ultrasound as described previously (Trudinger *et al.* 1985a). The systolic:diastolic ratio (A B ratio) of the umbilical artery waveform was measured, graded and plotted using our normal range (Thompson *et al.* 1988) The results were divided into four groups according to the value of the AB ratio; normal if below the 95th centile; elevated if between the 95th and 99th centile; high if above the 99th centile; and extreme if diastolic flow velocities were absent.

If three or more FVWs had been recorded the trend of the results was assessed and designated normal if at least two of the last three AB ratios were below the 95th centile value. The trend was designated abnormal if at least two of the last three AB ratios were above the 95th centile, and this group was further subdivided. An abnormal improving trend was present if the last two values relative to earlier studies were decreasing and moving closer to the 95th centile value An abnormal and worsening trend was present if these values were increasing relative to the 95th centile.

Patient details and FVW results were recorded prospectively on standard cards at the time of the Doppler study, and outcome details were entered on these cards at the time of delivery. These data were transferred to a computer for analysis using the Minitab statistical package. For continuous variables, differences between groups were analysed using analysis of variance (ANOVA) with Bonferroni correction for multiple comparisons. Data about duration of stay in neonatal nursery were first normalised by logarithmic transformation (Zar 1984). Categorical data were examined using the χ^2 test.

Results

Table 2 shows the outcome of all 2178 pregnancies subdivided according to the result of the last umbilical artery FVW. The gestational age at

Table 1.

Principal reason for study	No of subjects
Suspected fetal compromise	756
Hypertension	476
Antepartum haemorrhage	125
Preterm labour	74
Prelabour rupture of membranes	43
Diabetes	171
Rhesus incompatibility	15
Poor obstetric history	135
Systemic lupus erythematosis	35
Other	348

Table 2. Outcome in 2178 pregnancies by result of last umbilical artery flow velocity waveform (FVW) study

		Systolic·diastolic ratio centile			
	Whole group	<95th (normal)	95–99th (elevated)	>99th (high)	ADF (extreme)
No. of pregnancies	2178	1650 (76%)	193 (9%)	239 (11%)	96 (4%)
Gestational age at delivery (weeks)	37·7	38·3	37·6***	35·8****	31·1****
Onset of labour					
Spontaneous	790	691 (42%)	56 (29%)	35 (15%)	8 (8%)†
Induced	818	642 (39%)	86 (45%)	85 (36%)	5 (5%)†
Mode of delivery					
Elective CS	570	317 (19%)	51 (26%)	119 (50%)	83 (86%)†
Vaginal	1371	1145	122	95	9
Emergency CS	237	188	20	25	4
Newborn					
Birthweight (g)	2875	3097	2713****	2148****	1198****
Length (cm)	47·8	48·8	47****	44·2****	37·6****
Ponderal index	26·0	26·4	25·9	24·6****	21·8****
Birthweight centile	36·2	41·9	27·0****	15·1****	9·0****
No. of SGA infants					
<10th centile	588 (27%)	293 (18%)	73 (38%)	144 (60%)	78 (81%)†
<5th centile	389 (18%)	165 (10%)	44 (23%)	111 (46%)	69 (72%)†
Apgar score ≤6					
At 1 min	531 (24%)	335 (20%)	53 (27%)	78 (33%)	65 (68%)†
At 5 min	131 (6%)	62 (4%)	16 (8%)	27 (11%)	26 (27%)†
Admission to NICU					
No. admitted	548	303	45	113	87†
Mean stay (days)	18·5	10·0	18·9*	25·0****	43·7****
Perinatal deaths					
Stillbirths	21	8	4	3	6
Neonatal deaths					
Day 0–7	38	16	4	9	9
Day 8–28	10	2	0	0	8
PNM rate/1000	31·7	15·8	41·5	50·2	239·6†
Corrected PNM	18·2	7·9	21·2	13·0	206·5†
Major fetal anomaly					
Total no.	61	27	9	16	9†
Survived ≥28 days	31	14	5	7	5
Neonatal deaths	24	11	3	7	3
Stillbirths	6	2	1	2	1

Results shown are mean values or no (% of group) as appropriate. Significance of difference compared with the normal group *$P<0·05$; **$P<0·01$; ***$P<0·001$; ****$P<0·0001$ (ANOVA with Bonferroni correction); †$P<0·0001$ (χ^2 for categorical data)

ADF = absent diastolic flow; CS = caesarean section; corrected PNM = perinatal mortality rate/1000 total births corrected for fetal anomaly.

delivery, need for operative delivery, size at birth (weight, length and ponderal index measured as weight/length^3×100) and the duration of neonatal intensive care differed significantly between pregnancies associated with abnormal FVWs and those with normal FVWs. This significant difference remained when analysis of covariance was performed to eliminate the effects of differing gestational age in the four Doppler result groups. Fetal growth retardation (low centile weight) was more likely in the groups with an abnormal FVW. To control further the influence of preterm delivery, outcomes such as mode of delivery, birthweight, neonatal intensive care unit (NICU) admission and perinatal mortality were examined according to gestational age at delivery. The results are shown in Table 3. Pregnancies with an abnormal umbilical artery FVW resulted in infants

Table 3. Outcome of pregnancies delivered before 37 weeks gestation according to degree of abnormality of the umbilical artery flow velocity waveform systolic: diastolic ratio

Gestation at delivery (weeks)	Systolic:diastolic ratio centile <95th (normal)	 95–99th (elevation)	 >99th (high)	 ADF (extreme)
		No. of pregnancies		
28–30	28	11	23	40
31–33	92	14	38	26
34–36	167	25	54	14
		Mean birthweight (g)		
28–30	1364	1154	1014****	954****
31–33	1875	1750	1514***	1416****
34–36	2641	2295*	2027****	1799****
		Mean birth length (cm)		
28–30	38·7	37·7	35·8	35·9
31–33	43·1	41·2	40·0***	38·2****
34–36	47·0	45·6**	43·7****	41·6****
		No. (%) of SGA infants (<10th centile)		
28–30	5 (18%)	4 (36%)	15 (65%)	32 (80%)†
31–33	13 (14%)	6 (43%)	21 (55%)	21 (81%)†
34–36	25 (15%)	10 (40%)	34 (63%)	12 (86%)†
		Duration of stay NICU (days)		
28–30	37·4	41·2	50 6*	68·8**
31–33	13·2	18·5	25·5***	20·8*
34–36	5·3	6·8	12·8*	8·9

Significance of difference compared with the normal group *$P<0{\cdot}05$; **$P<0{\cdot}01$; ***$P<0{\cdot}001$; ****$P<0{\cdot}0001$ (ANOVA with Bonferroni correction); †$P<0{\cdot}0001$ (χ^2 for categorical data).
AFD = absent diastolic flour; SGA = small for gestational age

who were smaller and required a longer period in the NICU.

The trend in the umbilical artery FVW pattern in the 794 women studied serially was examined and the results are shown in Table 4. Pregnancies with abnormal FVWs were associated with lower

Table 4. Pregnancy outcome in relation to trend in serial umbilical artery flow velocity waveform AB ratios

Variable	Pattern of serial FVW AB ratios Normal	 Abnormal/improving	 Abnormal/deteriorating
Total no. of pregnancies	567	117	110
Gestation at delivery (weeks)	38·5	37·5***	34 5****
Birthweight (g)	3164	2708****	1906****
Centile birthweight	43·8	26·5****	12·4****
SGA (<10th centile) *n* (%)	97 (17%)	47 (40%)	78 (71%)†
Admission NICU *n* (%)	101 (18%)	27 (23%)	65 (59%)†
Duration stay NICU (days)	6·1	11·1	34****
Perinatal mortality			
Number	7	2	7
Rate per 1000	12·3	17·1	63·6†

Results shown are mean values or no (% of group) as appropriate. Significance of difference compared with the normal group *$P<0{\cdot}05$, **$P<0{\cdot}01$; ***$P<0{\cdot}001$; ****$P<0{\cdot}0001$ (ANOVA with Bonferroni correction); †$P<0{\cdot}0001$ (χ^2 for categorial data).

Table 5. The outcome characteristics for each year of the study

	Year					
	1983	1984	1985	1986	1987	1988
Total no. of pregnancies	443	396	292	361	342	344
Mean gestation at delivery (weeks)	37·7	37 7	37 6	37·9	37·6	37 5
Mean birthweight (g)	2885·2	2901·3	2808 0	2908·7	2847·5	2879·5
Mean birthweight centile	37·0	37·1	33·3	36·3	34·7	37·6
No. (%) of SGA infants	105 (24%)	104 (26%)	90 (31%)	95 (26%)	105 (31%)	91 (26%)

SGA = small-for-gestational age (<10th centile).

birthweight babies who spent more time in neonatal intensive care than pregnancies with normal FVWs. The differences were more pronounced in the group with a deteriorating AB ratio.

Since the Doppler results were not clinically available during the early part of this study we examined the outcome characteristics for each year of the study There were no significant difference in mean gestational age at delivery, birthweight, centile birthweight and frequency of SGA infants (Table 5). We examined perinatal mortality for the years before (1983–84) and after (1985–88) the conclusion of a previously reported clinical trial which assessed umbilical Doppler studies (Trudinger *et al.* 1987). After that trial Doppler umbilical studies were freely promoted in our institution In the early years (839 pregnancies) the perinatal mortality was 38/1000 and in the later period (1339 pregnancies) it was 28/1000. Although the neonatal death rate did not differ between these two secular groups (23 compared with 22/1000), the fetal death rate was significantly less in the later group (15 compared with 6/1000, $P = 0{\cdot}026$).

Discussion

In this paper we report the outcome characteristics in a large group of pregnancies at high risk of fetal compromise investigated with Doppler umbilical artery FVW studies. There was a highly significant association between abnormal FVWs and the need for obstetric intervention, fetal size at birth (absolute and centile weights) and neonatal condition assessed by the duration of intensive neonatal care required. Previously reported information on neonatal condition after birth in relation to Doppler studies is limited. An increase in the occurrence of necrotizing enterocolitis has been reported in association with a very abnormal fetal aortic waveform (Hackett *et al.* 1987), but this observation was not controlled for gestational age. In this report we have also demonstrated that fetal deaths decreased coincident with the wide clinical use of umbilical Doppler studies. Whilst there may be other contributing factors, this finding parallels our observation in twin pregnancies (Giles *et al* 1988).

Ideally, a clinical test of fetal welfare should not be used widely until its role has been assessed in randomized controlled trials. However, it is necessary to know what the test is predicting in terms of fetal and neonatal condition before the appropriate trial can be designed to test clinical management strategies. The association between fetal growth failure and abnormal Doppler umbilical artery FVWs is clearly demonstrated. The large size of the present study population is sufficient to demonstrate that at all gestations the requirement for neonatal intensive care is much greater in association with abnormal umbilical artery FVWs. This information is now available for the design of tests of management strategies. The recent demonstration that low-dose aspirin therapy improves fetal growth (higher birthweight) in pregnancies with abnormal umbilical artery FVWs (Trudinger *et al.* 1988) is relevant here. Another end point which should be examined after this therapy is the possible reduction in requirement for neonatal intensive care.

In analysing the predictive ability of Doppler umbilical studies we have addressed two important confounding variables: gestational age at delivery and clinical intervention. Fetuses from pregnancies with abnormal artery FVWs were smaller and required more neonatal intensive care independent of gestational age. Since the studies in the later part of this series were available to the managing clinician it could be argued that the abnormal study precipitated earlier intervention with delivery of a small infant requiring neonatal intensive care. That this was not so is demonstrated by the similarity in outcome characteristics throughout the study period. In our randomized trial (Trudinger *et al.* 1987) we demonstrated that the availability of Doppler studies resulted in prolongation of high risk pregnancies.

The results of our investigation support the use of Doppler umbilical FVW studies as a first fetal welfare investigation or 'doorway' test with a positive result leading to intensive surveillance with other fetal studies. Doppler umbilical studies provide unique information to complement other tests of fetal welfare in common clinical use, such as fetal heart rate monitoring and the use of biophysical profile scores Comparison of fetal outcome in the group with an elevated (95–99th centile), high (>99th centile), or extreme (absent diastolic flow) AB ratio suggests the possibility of grading fetal risk by the degree of waveform abnormality. Neonatal problems were far more likely if the waveform was high or extreme. However, we are unhappy with this approach as the umbilical waveform detects a placental vascular lesion. An effect on fetal condition in this truly at risk group should be sought using other fetal tests before resorting to delivery, as some fetuses in the high and extreme groups have a good outcome. A number of authors (Rochelson *et al.* 1987a; Woo *et al.* 1987) have used absent diastolic flow velocities as an index of an extremely abnormal waveform and suggested that it constitutes a 'watershed' for fetal risk. The outcome in our high and extreme groups was similar between 28 and 32 weeks and we prefer the statistical definition based on centile values of the extreme case rather than a finding which varies with gestational age and may occasionally result from error of technique (Trudinger 1987).

The trend of umbilical Doppler results proved a very useful measure of neonatal morbidity in those patients with serial studies. A decreasing systolic diastolic ratio was associated with good outcome even if the values were outside our normal range. Such a result suggests continuing placental growth. Serial studies may be helpful in determining the effect of therapies like bed rest. Serial studies are also important in identifying the false positive results Two recent reports have assessed umbilical Doppler FVWs in normal unselected pregnancies (Beattie & Dornan 1989; Schulman *et al* 1989) and demonstrated no correlation with size at birth. In another study no correlation with fetal outcome apart from birthweight was reported (Hanretty *et al.* 1989) Such studies have a very low statistical power because fetal compromise is infrequent. Pregnancies with low growth potential in which both fetus and placenta are small and the fetus is not being deprived by 'placental insufficiency' constitute a much greater proportion of identified pregnancies. Our results suggest that serial (weekly) studies in such unselected screening programmes would eliminate this problem.

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Risk of recurrence after myomectomy

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Summary. The risk of recurrence of uterine myomas was analyzed in 622 patients who underwent myomectomy between 1970 and 1984 at the First Department of Obstetrics and Gynecology of the University of Milan. The cumulative 10-year recurrence rate was 27%, and this increased steadily up to the end of the observation period. Differences were not observed in frequency of recurrence by age at diagnoses or by the site of the myomas at surgery. Patients with a single myoma tended to experience a lower rate, but this finding was not statistically significant. Women who gave birth to a child after myomectomy had a 10-year recurrence rate of 15%, against 30% for those who did not; this difference was statistically significant.

Uterine myomas are the most common pelvic tumours in women. In principle, they can cause infertility, distorting the uterine cavity or occluding tubes and altering vascularization. Women with these tumours experience menorrhagia, iron deficiency anaemia and pelvic pain (Buttram & Reiter 1981). When these conditions occur during reproductive life, myomectomy is considered.

In some women, surgery is followed by regrowth of the neoplasm. However, quantitative information on the risk of recurrence is largely imprecise. Clinical studies have reported recurrence rates ranging from 5 to 30% (Buttram & Reiter 1981). This wide range may be explained by different criteria used in diagnosis and/or deficiencies in long-term follow-up. The effect of potential prognostic factors has still not been properly investigated.

We have studied a large consecutive series of women undergoing myomectomy between 1970 and 1984 at the First Department of Obstetrics and Gynecology of the University of Milan.

Subjects and methods

Between January 1970 and December 1984, 622 women (mean age 33 years, range 22–44) underwent myomectomy for at least one leiomyoma larger than 5 cm at the First Department of Obstetrics and Gynecology of the University of Milan. The indication for treatment was recurrent menorrhagia or pelvic pain (including pressure symptoms and chronic pelvic pain in subjects with fibroids) in 59%, infertility in 36% and recurrent miscarriage in 5%.

Intracavitary myomas, which might have remained undetected during surgery, were sought preoperatively, by systematic hysterosalpingography until 1978 and, thereafter, usually by intraoperative hysteroscopy before the start of laparotomy.

Myomectomy was performed by an atraumatic technique, in an irrigated field in order to prevent peritoneal adhesions. Incision of the myometrium was performed with electrosurgery, preferably along the median sagittal plane

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Table 1. Distribution of 622 women undergoing myomectomy according to selected characteristics. Milan, Italy 1970–1984

	Patient	
Characteristic	*n*	(%)
Age (years)		
≤24	23	(4)
25–29	124	(20)
30–34	231	(37)
35–39	207	(33)
≥40	37	(6)
Parity		
0	448	(72)
1	116	(19)
2	49	(8)
≥3	9	(1)
Miscarriages		
0	514	(83)
1	76	(12)
2	22	(4)
≥3	10	(2)
No. of myomas*		
1	300	(50)
2	99	(16)
3	65	(11)
≥4	137	(23)
Site of myomas*		
Subserous	355	(58)
Intramural	174	(29)
Submucous	52	(9)
Intraligamentous	28	(5)

*Some observations are missing.

of the uterine body. Accurate haemostasis was obtained with the use of a bipolar coagulator. To lessen the formation of adhesions, corticosteroids and antibiotics were given routinely during the recovery from surgery. No major complication or death occurred after surgery.

The distribution according to age, reproductive history and the clinical characteristics of myomas is presented in Table 1.

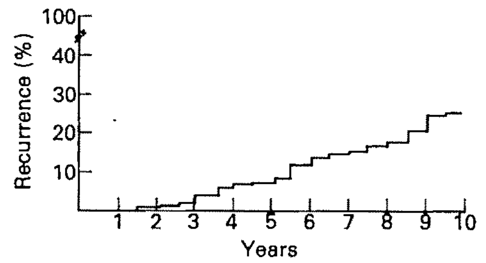

Fig. 1. Overall 10-year probability of recurrence after myomectomy (*n* = 622; 84 recurrences)

The women returned for follow-up visits every 12 months. Subjective symptoms were assessed, in particular the appearance or worsening of pelvic pain, dysmenorrhea and menorrhagia. A pelvic examination was performed at which the size and outline of the uterus was assessed. All the patients with abnormal pelvic finding and also all those with normal pelvic examination but suspect symptomatology underwent pelvic ultrasonography to confirm or exclude recurrence.

Data analysis

The cumulative probability of recurrence was calculated by the product limit methods and the curves were compared by the log-rank test (Peto *et al.* 1977). The event data used in the computation were the dates of myomectomy, first diagnosis of recurrence and last follow-up visit. In order to provide quantitative estimates of the risk of recurrence according to the various considered prognostic factors and to allow for their potential reciprocal confounding effect, multivariate relative risks of recurrence (and corresponding 95% confidence intervals), in relation to arbitrarily defined reference categories, were computed for selected factors by the proportional hazard model given by Cox (1972).

Results

A total of 120 patients (19%) were lost to follow-up and consequently censored at the time of their last follow-up visit (see data analysis). All other women were followed regularly with a median follow-up of 102 months. The characteristics of the women lost to follow-up were largely similar to those of the women who were followed regularly. For example, the mean age of the women lost to follow-up was 32 years, and 30% were parous compared with 33 years and 28%

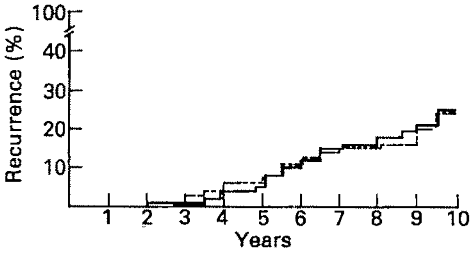

Fig. 2. Comparative 10-year probability of recurrence after myomectomy according to age: —— ≤30 years (*n* = 147; 24 recurrences); - - - - >30 years (*n* = 475; 60 recurrences.)

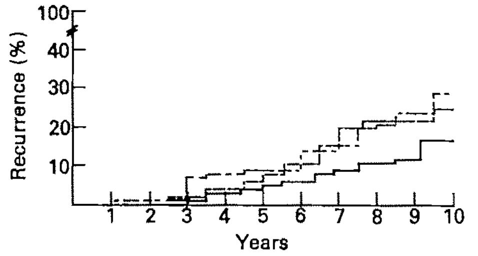

Fig. 3. Comparative 10-year probability of recurrence after myomectomy according to number of myomas —·— 1 ($n = 300$; 38 recurrences); - - - - 2–3 ($n = 164$; 25 recurrences); —— 4≥ ($n = 137$; 21 recurrences).

for those who continued in the study. Similarly, in the group lost to follow-up a mean of two myomas was removed and in 59% the larger (or only) myoma removed was subserous; the corresponding findings were 2 and 56% in the followed patients. Women from all over Italy are referred to our centre for myomectomy. Thus, although it is difficult to quantify the reasons why women did not return for follow-up visits, the main reason for most of them was the great distance between where they lived and the hospital.

The cumulative 10-year recurrence rate after myomectomy was 27%, and increased steadily with time up to the end of the period considered (this estimate is based on 84 observed recurrences, Fig. 1). The recurrence rate was similar in women under or over 30 years of age, 25% and 24% respectively ($\chi^2 = 0{\cdot}12$, $P = 0.73$, Fig. 2). When the analysis was based on different subgroups, according to number of myomas removed at myomectomy, women with a single fibroid tended to experience a lower rate; this finding was of borderline statistical significance (χ^2 trend adjusted for age 3·76, $P = 0{\cdot}06$, Fig. 3).

The prognostic significance of a full-term pregnancy after myomectomy is presented in Fig. 4. Women who gave birth to a child had a 10-year recurrence rate of 16%, but those who did not had a rate of 28% (χ^2 adjusted for age = 3·96, $P = 0{\cdot}05$). Being parous or nulliparous at myomectomy did not affect the risk of recurrence, nor did the site of the myomas (data not presented).

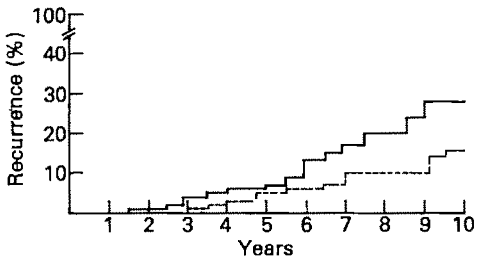

Fig. 4. Comparative 10-year probability of recurrence after myomectomy according to occurrence of a successful term pregnancy: —— no ($n = 477$, 66 recurrences); - - - - yes ($n = 145$; 18 recurrences).

Table 2 gives the multivariate relative risk of recurrence in strata of age, number of pregnancies before myomectomy, number of myomas removed and the occurrence of a full-term pregnancy after myomectomy. No association emerged between risk of recurrence, age, and number of pregnancies before myomectomy, but, compared to women from whom a single myoma was removed, the risk was 1·2 in those with two or three and 2·1 with four myomas removed. Compared with women who did not give birth to a child after myomectomy, those who did had a relative risk of recurrence of 0·6 (95% CI 0·4–0·9).

Discussion

This study provides more precise information than was available previously, on the risk of recurrence after myomectomy. In this series of over 600 women who underwent myomectomy the recurrence rate was 27% at 10 years. This percentage did not vary with the age of the women at the time of surgery, but was lower for

Table 2. Multivariate relative risk (and 95% confidence interval) of recurrence in strata of age, parity, number of pregnancies and number of removed myomas. Milan, Italy 1970–1984.

	Relative risk*	(95% CI)
Age (years)		
≤30	1 †	
>30	1·0	(0·8–1·1)
Number of pregnancies before myomectomy		
0	1 †	
≥1	1·0	(0·8–1·21)
Number of myomas removed		
1	1 †	
2–3	1·2	(0·9–1·51)
≥4	2·1	(1·7–2·8)
Pregnancies after myomectomy		
0	1 †	
≥1	0·6	(0·4–0·9)

*Derived from logistic model including terms for the above listed variables.
†Reference category.

Table 3. Recurrence rates after myomectomy in the literature.

Study	No. of patients	Length of follow-up (years)	Recurrences n	(%)
Weiss (1926)	224	3–7	17	(8)
Bonney (1931)	210	≥2	8	(4)
Miller & Tyrone (1933)	94	3–10	8	(9)
Conseller & Bedard (1938)	523	≥2	111	(21)
Finn & Muller (1950)	274	≥2	48	(23)
Munnel & Martin (1951)	236	–	49	(21)
Brown *et al.* (1956)	234	≥2	66	(28)
Davids (1957)	301	–	24	(8)
Rubin (1958)	222	–	37	(17)
Malone (1969)	125	5–10	59	(47)
Loeffler & Noble (1970)	116	≥1	33	(28)
Babaknia *et al.* (1978)	46	≥2	13	(28)
Buttram & Reiter (1981)	42	≥1	6	(14)

women who gave birth to a child after myomectomy, and for those with a single myoma, although the difference was of borderline statistical significance. These estimates should not be greatly affected by bias but some of the limitations of the study will be briefly discussed.

The major drawback of this study is the high percentage of women (about 20%) lost early to follow-up. However, their distribution by age, reproductive history and the number and localization of their myomas was largely similar to those for whom follow-up information was available.

Although the study period covered about 15 years, the general clinical management of patients did not change markedly during this time during which the surgical procedures were performed under the supervision of one of the authors (G.B.C.). Analyses based on subdivisions of the follow-up period did not show marked differences.

Opinion is still divided on the significance of myoma regrowth after myomectomy. Some authors (Finn & Muller 1950) view it as persistent disease, that is, the result of an unintentionally incomplete operation that left undetected myomatous formations *in situ* in the myometrium.

Babaknia *et al.* (1978) consider that the reappearance of myomas is inversely related to the efficiency of the operator in searching for and removing minimal lesions during the first operation. On the other hand, an individual genetic predisposition has been hypothesized which would absolve the gynaecologist; despite complete removal of all fibroids at surgery, some uteri would still have scattered cells that could later develop into myomas. In such cases it is correct to talk of recurrence.

Unfortunately, for organizational reasons and because of cost, our follow-up consisted of clinical and ultrasound examinations rather than systematic ultrasonography. However, recurrences were confirmed by sonography, and other pelvic swellings and uterine enlargement due to diffuse hypertrophy or adenomyosis were excluded. Moreover, since women with symptoms suggesting recurrence but with normal pelvic organs on clinical examination underwent ultrasonography, small symptomatic lesions, such as small submucosal myomas, did not remain undiagnosed. Consequently, even though not all women had an ultrasound follow-up, our study will have missed only those small intramural myomas not detectable on clinical pelvic examination and not causing symptoms.

Published studies show marked differences in the probability of recurrence after myomectomy (Table 3). Early reports generally showed rates around 5 to 10% (Berkeley *et al.* 1983; Bonney 1931; Brown *et al.* 1956; Conseller & Bedard 1938) but, more recently, recurrence rates of 25–35% have been observed (Finn & Muller 1950; Loeffler & Noble 1970; Malone 1969), in agreement with the results of our research. These differences can be at least partly explained by the criteria for diagnosis of recurrence (ultrasonography is more sensitive than clinical assessment) and by deficiencies in long-term follow-up. The number of myomas removed at myomectomy has been associated positively with the risk of recurrence (Garcia & Tureck 1984). A similar trend was observed in our series, but this was of borderline statistical significance.

A successful term pregnancy after myomectomy was the major prognostic determinant; women who gave birth to a child had about half the risk of recurrence. This association was confirmed when an analysis was conducted in the subgroup of women actively trying to conceive and was not explained by difference in the baseline distribution of the characteristics of women who conceived and of those who did not. In fact, the estimated multiple logistic relative risk of recurrence (including terms for age, obstetric history and number of myomas removed) was 40% lower in women who gave birth to a child. Although there is no obvious biological explanation of this finding, it compares well with epidemiological data from the United Kingdom (Ross *et al.* 1986) and Italy (Parazzini *et al.* 1988), showing a protective effect of pregnancy on the risk of development or the growth of uterine myoma.

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Obstetric accidents: the patient's perspective

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Summary. Cases from the files of Action for Victims of Medical Accidents which had resulted in stillbirth, perinatal or neonatal death and long term mental or physical handicap were reviewed. In 41 cases there was both a detailed letter from the parents and an independent review by a senior obstetrician. The reviewer's main criticisms were of inadequate fetal heart monitoring, lack of involvement of senior staff and inadequate records. The fetal heart trace was missing in 7 cases and over half of the remaining 34 traces available were misinterpreted or not acted on. In 17 cases junior doctors failed to recognize fetal distress and managed a delivery that they did not have the experience to deal with. In a further 6 cases, senior staff were called but did not come. Records were criticized for being incomplete, illegible or missing. In a few cases unjustified alterations appeared to have been made. Women reported that on some occasions staff ignored their worries, were unsympathetic and gave too little information. Some parents also experienced considerable difficulty in obtaining a clear explanation of the nature and cause of their child's condition.

Medical accidents have been largely ignored as an area of research We do not know how often they occur or why they happen, nor do we understand the effects of the accident on the patients who suffer them (Vincent 1989). With the growing emphasis on audit the neglect of accidents as an area of research is increasingly striking. Any serious attempt to monitor standards of care should include an investigation when things have gone wrong.

Obstetricians are more forward looking in this regard than many clinicians (Orr 1989; Brown 1989). The triennial reports on the confidential enquiries into maternal deaths in England and Wales published by the Department of Health since 1952–1954 were an important step as they assess the proportion of cases where care might not have been adequate. Similar enquiries into perinatal deaths have been recommended by the Royal College of Obstetricians & Gynaecologists and have been introduced by some regional health authorities. However, while confidential enquiries (Lunn & Mushin 1982; Buck *et al.* 1987) comment on examples of sub-standard care, they do not give a detailed account of the errors made and the reasons for them. One of the few studies to look specifically at accidents in obstetrics is a recent review of cases from the Medical Protection Society (Ennis & Vincent 1990). Mismanagement of forceps, inadequate cardiotocographic (CTG) monitoring and lack of involvement of senior staff were found to be frequent factors in these accidents.

In the present study, we review a series of obstetric cases from the files of Action for Victims of Medical Accidents (AVMA). Our aims were to determine the factors involved in these accidents and to see if independent reviewers,

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employed by the plaintiffs, would indentify similar types of problems as those consulted by the Medical Protection Society. We also included an assessment of the women's perceptions of the care they received and the attitudes of the hospital staff. We also classified and recorded criticisms of the records under review.

Methods

We studied all cases reported to AVMA from its formation in 1982 to the end of December 1988 where a child was either stillborn or suffered lasting physical or mental impairment from damage probably sustained during labour or delivery. We restricted our review to 41 cases for which there was both a detailed letter from one of the parents and a full report from an independent medical expert consulted by the patient's solicitor (a consultant obstetrician or professor of obstetrics).

AVMA receive a great many letters from parents of stillborn or handicapped children, but most of these cases do not proceed to litigation. Even if litigation is contemplated and an expert opinion sought, this may not be available to AVMA. The 41 cases are therefore only a small proportion of those who have consulted AVMA. However, we regarded an expert opinion as crucial to a valid assessment and deliberately restricted our sample.

From an initial survey of the cases we devised a standard report form to record:

(i) nature and cause of death/damage;
(ii) risk factors and warning signs;
(iii) expert criticisms of management of delivery,
(iv) mother's account of care offered and
(v) adequacy of medical records. (This form is available from the authors).

Subsequently, the cases were reviewed and the data recorded. Great care was taken to identify clearly the source of any information and to record only unambiguously stated criticisms. All criticisms reported below, except those made by the women themselves, were made by senior obstetricians not by the authors of this paper.

Results

1. *Patients*

(a) Risk factors and warning signs

The reviewers noted pre-eclampsia in five, threatened miscarriage in four and small stature in a further four cases. Whereas these factors do not necessarily constitute risk (many healthy babies are born to women of small stature), in these particular cases they were highlighted as risk factors by the expert reviewers. There may have been other risk factors, but the reviewers did not think them worthy of note.

(b) Outcome

Eight of the 41 babies died during labour or shortly afterwards. According to the independent reviewers the 33 surviving infants suffered longstanding mental impairment, motor impairment or, usually, both. Table 1 gives details of the outcomes.

Table 1. Degree of impairment of surviving infants

	Degree of impairment			
Impairment	None	Mild	Moderate	Severe
Mental	11	4	4	14
Motor	4	3	9	17

Table 2. Grade of staff managing the birth

Student midwife (supervised)	3
Midwife	8
SHO	10
Registrar	9
Senior registrar	1
Consultant	2
Doctor, grade unknown	8

The most common cause of death or impairment was assessed as being hypoxia (34 cases), with 20 of these resulting from a delayed caesarean section. Causes of hypoxia were cord entanglement, cord prolapse, inhalation of meconium, problems with anaesthesia (both inhaled and epidural), and placental abruption. A caesarean section was performed in 14 cases, often after considerable delay and after attempts at forceps delivery. Resuscitation was attempted in 18 In at least four cases the problems were considered to have been compounded by inadequate resuscitation of the baby.

2. *Staff present at delivery*

Table 2 shows the person primarily responsible for the delivery.

On two occasions a consultant was present, or available, even though an SHO managed the delivery. Student midwives were usually supervised, although sometimes in very high risk situ-

Table 3. Adequacy of fetal heart monitoring

Trace missing	7
Adequate monitoring	15
Abnormal trace not recognized	14
Abnormal trace—no action taken	5

ations. If cases where junior staff were supervised are excluded, we find that in nine cases no doctor was called or none arrived (the delivery being managed by midwives) and, in a further eight, that only an SHO was present at the delivery. In many cases experienced staff arrived late in the labour, usually only in time to limit the damage already done.

3. *Standard of care*

Criticisms were made by independent reviewers of the following aspects of care:

(a) Assessment of labour

Criticism was made by the expert reviewer of the adequacy of the vaginal examination in six cases; in a further two the examination appeared to have been adequately performed but no action was taken on the abnormal findings. The fetal position was incorrectly assessed in four cases. In an additional five cases labour was considered to be prolonged. Meconium was noticed in 13 cases. Another warning sign was blood loss in three cases. In all but seven cases the expert reviewer was able to note warning signs that should have alerted those present to the possibility of fetal distress. This suggests that some of these accidents may have been preventable.

(b) Fetal heart monitoring

The CTG trace was missing in seven cases. The quality of fetal heart monitoring was criticized in over half of the remaining 34 cases.

In 14 cases the doctor or midwife simply did not recognize an abnormal trace. In five the abnormality was noted, but no action was taken; the staff believing the machine to be faulty and so ignored the trace. In one instance, the monitor did prove to have a fault but in the other four, the baby was in genuine distress. No attempt seems to have been made to monitor the heart with a stethoscope while the machine was checked. In addition to fetal heart rate changes, staff failed to recognize meconium staining of the amniotic fluid in three cases. In several others, staff failed to take account of the severe pain the woman was experiencing or blood loss reported by the woman (see below).

(c) Absence of senior staff

Delivery by inexperienced staff was noted in 17 cases, generally because of the failure of midwives or junior doctors to recognize that the baby was distressed. For instance, a reviewer commented that the doctor was insufficiently experienced to recognize the warning signs of a prolonged second stage of labour and fetal distress. There is no comment in the case records that the consultant was notified nor indeed of any discussion with someone more senior.

However, not all the responsibility should be borne by junior doctors. In six cases (15%) a senior doctor was called but failed to arrive. In one of these cases he or she was uncontactable but, in the other five, they were contacted but did not come. In another four cases where the senior doctor did arrive, the independent expert commented on the length of the delay and its implications for the eventual outcome.

4. *Medical records*

(a) Missing and altered records

Reviewing cases were hampered both by the standard of records and the fact that they were often incomplete. Records were missing in 22% of cases: the CTG trace in seven, the nursing records in three, a substantial part of the medical notes in two and ultrasound records in a further two cases. Missing CTGs could have been removed for teaching purposes, or just lost. However, some instances of missing notes were harder to explain. Reviewers commented on a 'highly suspicious absence of notes' and 'rather selective loss of documents'. There were also suggestions that the notes had been tampered with in four cases and, in one case, the independent expert stated unequivocally that items and words had been altered in both the notes and nursing records.

(b) Adequacy of records

Some criticisms were made of the adequacy of the records that were kept in 26 (63%) of cases.

Signatures were illegible in 10 cases, and at times unclear in two. In four cases large sections of the notes were completely illegible. Inconsistencies, inadequate recording and inadequate labelling of observations were common, but occasionally deficient record keeping reached quite remarkable proportions. In two cases no record of the birth could be found at all.

5. *Mothers' perspective*

(a) Awareness of problems and attitude of staff

Table 4. Adequacy of medical records

	No of cases	%
Illegibility	14	34
Inconsistencies	11	27
Inadequate observations recorded	22	54
Inadequately labelled observations	7	17
No account of birth	2	5
Mixed with notes of other patients	3	7

In 13 cases the mother was aware, often before the staff that the labour was not progressing satisfactorily. Bleeding and excessive pain were the most common complaints. In 11 cases she communicated her worries to the staff, but in seven they failed to take her worry seriously—dismissing the pain or bleeding as unimportant. Women also complained that staff disregarded their wishes and feelings (10 cases), were unsympathetic (10 cases) and were unduly critical (4 cases). These might appear relatively minor complaints but it was clear from the letters that the memory of comments made by staff continue to distress some parents years later.

(b) Communication between staff and parents

Parents were also concerned about the lack of information given to them. Table 5 summarizes the principal comments.

The criticisms of lack of information are familiar (Ley 1989), and perhaps partly due to the pressure of work in a busy delivery suite. The failures to inform the parents of the diagnosis and its implications are more disturbing. In these cases the parents felt that there was undue delay in informing them of the tragic outcome. In some instances they also had considerable difficulty obtaining a clear explanation of their child's condition. Clearly the degree of handicap that may result from hypoxia or trauma at delivery is difficult to assess immediately. However, concern about the baby's possible prognosis should have been discussed with the parents.

Discussion

The results of this study confirm some of the main findings of our earlier study (Ennis & Vincent 1990); inadequate fetal heart monitoring and insufficient supervision of junior doctors were implicated in a high proportion of these accidents. Frequent criticisms were also made of the medical records, which were often incomplete or deficient. This means that some instances of sub-standard care may have gone unreported. The women involved, and their partners, reported a lack of response to information they gave staff and unsympathetic attitudes of staff.

As in our previous study it is clear that some junior doctors and midwives cannot recognize abnormal CTG traces. Where the trace was available for inspection, over half were misinterpreted with consequent delays in calling senior staff and arranging for caesarean section. Preliminary findings from a study of the training of junior doctors in obstetrics suggest that most receive only informal and inadequate training in CTG monitoring, and many are overconfident of their abilities (Ennis 1990). Murphy *et al.* (1990) have also reported that the interpretation of the intrapartum CTG presents problems for obstetricians. We suggest that a short formal introduction to CTG monitoring, with some clear guidelines for detecting an abnormal trace, would very much reduce the risk of this kind of case.

Failure to recognize fetal distress leads to the second major criticism made by expert reviewers. Junior doctors failed to call senior staff and so were managing situations that they did not have the experience to deal with. This may be because they failed to recognize the dangers, because they were overconfident or because they were anxious about calling senior staff. However, not all the responsibility rests with the junior doctors. In six cases the senior doctor, though called, failed to arrive. We cannot tell why they failed to come. It is possible that the junior doctor might not have conveyed the full gravity of the situation. It would be very interesting to know whether the juniors in these units are encouraged, or dissuaded, from contacting more senior staff whey they run into difficulties.

Reviewing cases was considerably hampered by inadequate or missing notes. Observations were inadequately recorded in over half the cases. For instance, in one case, 'The appear-

Table 5. Communication between staff and patient

	Doctor	Midwife
Too little information given	15	6
Reluctant to discuss	10	2
Failure to inform of diagnosis	8	2
Failure to discuss implications	7	–

ance of Type II dips occasioned no comment on the part of nurses or doctors and, indeed, there is no comment of any kind in the nursing notes between 1700 and 2145 h'. We suspect that very inadequate notes often mean inadequate care. At the very least, it means that a change of shift is potentially dangerous. As many obstetric units do not have a formal handover between doctors, the incoming doctor may be relying on the notes for information on the progress of labour. Notes were missing in 22% of cases, though whether they were lost or not released by health authorities is unclear. Plaintiffs are often frustrated by piecemeal disclosure of essential documents, yet a health authority as a duty to produce a complete set of the documents to which the plaintiff's advisers are entitled. More worrying are the suggestions that incriminating notes were destroyed, altered or invented. It is obviously legitimate to alter notes in the sense of correcting erroneous information, but the alterations cited here refer to the reviewer's suspicions that the records had been falsified.

Complaints of staff not providing enough information are common, and may often be excusable in a busy delivery suite. However, several letters from patients stated that they had considerable difficulty, later, in discovering the nature of their child's condition and the prognosis. Five parents wrote that their primary reason for litigation was to get a satisfactory explanation of how their child was damaged and why. A number of women suspected that something was wrong before the staff did. Obviously many women in labour may at times wonder whether their baby is in distress and, in the great majority of cases, their fears will prove to be groundless. However, in several of these cases, women in labour drew potentially alarming facts to the attention of the staff and were ignored. If they had been taken more seriously some of these incidents might have been avoided.

We are well aware that these cases are a tiny proportion of the births in the years covered by the study (Department of Health 1989). Giving birth is generally safe and usually carefully managed by experienced obstetricians and midwives. In contrast, in many of these cases the reviewers stated categorically that serious mistakes had been made. Does this simply indicate that doctors, like anyone else, occasionally make mistakes, or are there wider implications? The fact that common themes emerge, and that there are often several staff involved in any one case, suggests to us that the problems identified are more widespread. Only ocasionally, however, does a combination of errors, inexperience and circumstances have a tragic outcome.

The main point of studying accidents is not simply to cast blame, or identify negligent staff, but to highlight deficiencies in medical practice and provide guidelines for changes in practice and future research. The findings of our studies of records of accidents (Ennis & Vincent 1989) led us to investigate CTG monitoring in a further study. Preliminary results suggest that traces are often misinterpreted, and that some junior staff are overconfident and do not recognize their own deficiencies (Ennis 1990). It seems very possible that junior doctors are often left unsupervised in dangerous situations, and this is not confined to obstetrics. Future studies will be needed to determine the extent of these problems and the reasons for them.

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Psychiatric morbidity and acceptability following medical and surgical methods of induced abortion

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Summary. Ninety-one women were asked to complete a standardized multiple choice questionnaire (modified from the Edinburgh Postnatal Depression Scale) to screen for anxiety and depression before and after legal abortion in early pregnancy achieved either by using mifepristone in combination with a prostaglandin ($n = 54$) or by vacuum aspiration under general anaesthesia ($n = 37$). Before abortion over 60% in both groups had high scores (compatible with psychiatric morbidity), but after the abortion there was a significant and equal fall in scores so that by 1 month<10% of either group had high scores. There was no difference between the two groups. Both methods of abortion were acceptable to the majority of women, although only 75% of the medical group indicated they would have the same method if a future termination was ever required, compared with 94% in the surgical group. However, in 13 women who had experience of both methods, the medical approach was preferred by 10 (77%). Thus, medical abortion is acceptable to the majority of women and is associated with the same low rate of short term psychiatric morbidity as has been recorded with surgical methods of termination, despite greater patient involvement and awareness of the abortion process.

The incidence of psychiatric morbidity following induced abortion is low. A prospective study (Brewer 1977) reported a post abortion psychosis rate of 0·3 per 1000 women, considerably less than the incidence of puerperal psychosis in the same population. In a review of larger British studies, Gibbons (1984) concluded that major psychiatric sequelae were uncommon.

Common reactions to abortion are guilt, a sense of loss, sadness, grief, regret, self reproach and reduced self esteem. These, however, tend to be mild and short-lived, while a short circumstantial period of mourning is considered normal (Ford *et al.* 1971; Lazarus 1975). The majority of British women do not consider abortion a negative experience, nor regret their decision (Lask 1975), while a review of the recent American literature supports the same view (Lazarus & Stern 1986).

The fear that liberalization of abortion laws, and the more widespread availability and use of abortion, might induce serious emotional and psychological consequences have not been borne out by studies either in this country or the USA. Indeed, there is evidence to suggest that compulsory parenthood may have a detrimental effect on the mothers' mental health, and also on the emotional, social and intellectual development of children born after a refused abortion request (Walters 1980).

A number of risk factors have been identified which may predispose toward psychiatric morbidity among women having abortion, while dif-

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ficulties in access or unsympathetic attitudes by medical staff may adversely affect the outcome (McCance *et al.* 1975).

The recent development of a safe alternative to surgical termination may be expected to make a considerable impact on practice in this country. The combination of the antiprogesterone drug mifepristone and a prostaglandin has been shown to be safe and effective in three large trials (Dubois *et al.* 1988; WHO, 1989; UK Multicentre Trial 1990) and is likely to be widely used when the French manufacturers of mifepristone (Roussel-Uclaf) obtain a product licence in this country. Although initial experience of acceptability is encouraging (Urquhart & Templeton 1988), and there appears to be strong support among women for this development, medical termination involves more patient participation than surgical approaches, with greater awareness of the abortion process and possibly more discomfort.

In this study we have assessed anxiety, depression and associated feelings before and after medical and surgical termination, as well as comparing the acceptability to women of the two methods.

This study had the approval of the local ethics committee.

Subjects and methods

All women were eligible for termination under the terms of the 1967 Abortion Act. Each had a viable singleton pregnancy of gestation less than 64 days and was in good health. There were no exclusions on the basis of age or parity.

Fifty four women who were offered and accepted medical abortion using mifepristone and prostaglandin (UK Multicentre Trial 1990) were asked to participate in the study. All agreed. During the same time period 37 consecutive women having surgical termination also agreed to participate. The two groups were similar in age, parity and gestation (Table 1), but whereas the women who had medical abortion were offered a choice of method, the women who had surgical termination were not.

Questionnaire

A multiple choice questionnaire was based on the 13 item Edinburgh Postnatal Depression Scale (EPDS). This scale was developed after extensive pilot work had indicated the limitations of other psychiatric screening methods when used in or around the time of pregnancy (Cox *et al.* 1987). For this study the questionnaire was adapted for use in the pre- and postabortion period, and reworded accordingly Experience with the questionnaire was developed in a pilot study of 30 women having medical termination. The score range was 0–39 and a score of ≥15 was taken, on the basis of this experience, to indicate those women who had clinically evident feelings of anxiety and depression.

In the study the questionnaire was administered to all 91 women two days before termination, and also one and four weeks after termination. At the 1-week follow-up visit the women were also asked about unpleasant side effects and questions relating to the acceptability of the procedure.

Statistical analysis

Comparison between the two groups was made by the χ^2 or unpaired Student's *t*-test, using the Minitab Statistical Package (Pennsylvania State University).

Results

All 91 women completed the questionnaire before the termination. The rates of attendance for follow-up were high in both groups. Of the 54 women having medical termination, 48 (89%) attended for the 1-week review and 42 (78%) for the 4-week review. Similarly, of the 37 women having surgical termination 34 (92%) attended for the 1-week review and 33 (89%) for the 4-week review.

The questionnaire scores are given in Table 2. In each group there was a wide range of scores, but the mean score before termination was similar in the two groups, 15·8 for those having medical termination and 17·4 for those having surgery. One week after the termination there was a significant fall in the scores ($P<0{\cdot}001$) and this was similar in both groups. There was a further fall in mean scores in both groups at the 4-week follow-up. Similarly the proportion of women with high scores (>15) fell significantly after abortion. Among women having medical termination 33 (61%) had a high score in the pre-abortion assessment, and at 1 and 4 weeks the numbers were 7 (15%) and 4 (9%) respectively. Similarly, in the surgical group the proportion

Table 1. Characteristics of the women studied

	Medical termination (n = 54)		Surgical termination (n = 37)	
Age (years) Mean (SD)	24·3	(5·7)	23·7	(7·0)
Gestation (days) Mean (SD)	53·4	(6·6)	56·7	(5·4)
Primigravidae n (%)	37	(69%)	28	(76%)

was 25 (68%) falling to nine (26%) and three (6%) respectively. The fall in high scorers was significant in both groups (P<0·001), but there was no significant difference between the groups.

At the 1-week follow-up visit women were asked whether the method they had experienced would be acceptable if a future termination was ever required. In the medical abortion group, 36 of the 48 women replied that the method was acceptable in this respect (75%) while among those having vacuum aspiration, 32 of the 34 women indicated that the method was acceptable (94%). This difference was statistically significant (P≤0·01). There was a tendency for the women who did not respond positively to medical termination to be younger, nulliparous, to have required more analgesia and to have seen the products of conception. However, the numbers were small and statistical significance on each of these points was not reached. Those who found the medical method acceptable quoted reasons such as 'awareness of what was happening', 'more in control', 'avoidance of anaesthesia', and 'more discrete'. Thirteen women having medical termination who had a previous surgical termination and, hence, had experience of both methods, were asked which method they would prefer, if a future termination was ever required. Ten (77%) indicated that they preferred the medical method, while one did not and two were undecided.

Discussion

It has been demonstrated (Cox *et al.* 1987) that the Edinburgh Postnatal Depression Scale is a valid, reliable screening test for psychiatric morbidity and is sensitive to changes over time. Our modified version of the scale was used to make an objective assessment of the woman's psychological state before and after two different methods of early abortion. Women who were recruited for the study were followed up primarily for medical reasons (to confirm the abortion was complete and discuss contraception) and in this way any bias toward women with psychiatric morbidity was avoided. Follow-up attendance rates were high, and similar in both groups, removing another source of bias. The fall in screening test scores and, particularly, in the percentage of high scoring individuals in both groups, confirmed the clinical impression, and the findings of others, that induced abortion is not associated with an increase in psychiatric morbidity, at least in the short term. In our study, less than 10% of women had high scores 1 month after termination, and feelings of pre-abortion guilt rapidly diminished in intensity during the follow-up period. There was no evidence of any difference between those having medical or surgical abortion in terms of psychiatric morbidity, and both groups appeared to cope with the abortion equally well. A similar minority in each group remained distressed, and had feelings of regret about their decision.

However, although the acceptability of both procedures was high, it did appear that significantly more women found the surgical method of termination acceptable, and the reasons for this require further investigation. There was a tendency among those who found the medical procedure unacceptable to be younger, nulliparous and to have had problems with the pro-

Table 2. Edinburgh Postnatal Depression Scale questionnaire score before and after induced abortion

	Medical termination				Surgical termination			
	n	Mean	(SD)	[Range]	n	Mean	(SD)	[Range]
Pre-abortion	54	15·8	(7·2)	[1–30]	37	17·4	(7·2)	[4–31]
First follow-up (day 7)	48	8·1	(7·5)	[0–28]	34	9·7	(7·7)	[0–30]
Second follow-up (day 28)	42	5·5	(6·1)	[0–23]	33	6·1	(5·4)	[0–28]

cedure. Our experience suggests that more women suffer troublesome pain and bleeding after termination induced with mifepristone and prostaglandin, compared with vacuum aspiration, but it is of interest that 10 of 13 women who had experience of both methods indicated a preference for medical termination.

Thus, it appears that short term psychiatric morbidity is no more frequent after medical methods of termination than after surgical termination, despite the individual woman's awareness of and participation in the abortion process. Previous studies have shown that the non-surgical approach, using a combination of mifepristone and prostaglandin is safe and effective (UK Multicentre Trial 1990) and the present study has indicated that the procedure is acceptable to the majority of women. However, its acceptability is not as high as that associated with surgical termination. Further study may make it possible to identify the characteristics of women who are more suited to medical termination, and also to introduce clinical facilities that maximize the benefits while diminishing the physical and psychological sequelae.

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Post partum eclampsia and acute renal failure; treatment with prostacyclin. Case report

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Case report

After an uneventful first pregnancy, a healthy 20-year-old woman had a spontaneous delivery of a normal, full-term, male infant weighing 3·2 kg at a general practice maternity unit. The highest blood pressure recorded during pregnancy and delivery was 130/85 mmHg and urine testing had revealed only an occasional trace of protein. Over the first 4 h post partum, she became restless and complained of headache. Her blood pressure rose to 180/120 mmHg and a grand mal convulsion ensued. She was transferred to the local general hospital where intravenous infusions of hydralazine and diazepam were started. Blood pressure was maintained between 110/60 and 140/80 mmHg but four further convulsions occurred, the last at 17 h post partum. During this period oliguria and proteinuria (3+ on dipstick) developed. At 7 h post partum serum biochemistry was:- urea 6·5 mmol/l, creatinine 136 μmol/l, bilirubin 22 μmol/l, alkaline phosphatase 297 U/l (normal range 35–115 U/l), asparatate aminotransferase 1176 U/L (normal range 10–40 U/l), alanine aminotransferase 996 U/l (normal range 10–50 U/l) and uric acid 540 μmol/l. Haemoglobin was 11·3 g/dl, white cell count 11·9 × 10^9/l, platelet count 54 × 10^9/l. Urine output remained below 10 ml/h, and at 30 h post partum the patient was transferred to our hospital.

On arrival, the haemoglobin concentration had fallen to 10·1 g/dl and the platelet count to 49 × 10^9/l. The blood film was normal. A coagulation screen was normal except for slightly elevated fibrin degradation products at 10–40 μg/ml (normal <10 μg/ml). An intravenous infusion of prostacyclin (Flolan, Wellcome Medical Division, Crewe, Cheshire) was started and the rate was increased gradually to 4 ng/kg/min. At higher doses than this the patient complained of uncomfortable uterine contractions. Labetalol was also required to control hypertension. The platelet count improved steadily. Haemodialysis was first performed on the fifth day post partum when serum creatinine was 990 μmol/l and urea 31 mmol/l. Prostacyclin was discontinued when the platelet count reached 169 × 10^9/l on the seventh day postpartum. Urine output was less than 350 ml/day until the eighth day postpartum after which it improved rapidly. By the tenth day renal function was adequate without dialysis and transaminase levels were normal. A total of four haemodialyses had been required. By 3 weeks after delivery the patient had made a complete recovery.

She remained normotensive (blood pressure 120/70 mmHg) with normal renal function (serum creatinine 80 μmol/l, creatinine clearance 80 ml/min) and no proteinuria. She became pregnant again 2 years later and was treated empirically with prophylactic low-dose aspirin during pregnancy. This pregnancy was entirely uncomplicated.

Discussion

Eclampsia probably occurs in fewer than 1 in 1000 deliveries in Britain (Redman 1988). Postpartum eclampsia is well recognized and may follow an uncomplicated pregnancy (Samuels 1960; Bhose 1964). Haematological abnormalities (microangiopathic haemolytic anaemia, thrombocytopaenia) and hepatic dysfunction (elevated liver enzymes, jaundice) have been

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reported in up to 12% of patients with pre-eclampsia/eclampsia (MacKenna *et al.* 1983). This variant including haemolysis, elevated liver enzymes and low platelets has been termed the HELLP syndrome (Weinstein 1982). The microangiopathic haemolytic anaemia and thrombocytopenia are thought to be a consequence of interactions of erythrocytes and platelets with the damaged endothelium of small blood vessels. The liver abnormalities are believed to be the result of obstruction of blood flow in the hepatic sinusoids by fibrin (Weinstein 1985). Our patient had post-partum eclampsia with thrombocytopenia and abnormal liver function. There was no evidence of significant haemolysis.

Acute renal failure is now a very infrequent complication of pregnancy in the Western world. In one series, only 4 of 83 713 pregnancies were complicated by acute renal failure of any cause (Donohoe 1983). Severe pre-eclampsia/eclampsia is often associated with some degree of renal impairment but only rarely causes acute renal failure. The aetiology of renal failure in pre-eclampsia/eclampsia is complex and uncertain but may include vascular, glomerular and tubular abnormalities sometimes resulting in acute tubular necrosis (Grunfeld *et al.* 1980). There was only one case of irreversible renal failure among 12 patients with acute renal failure due to severe pre-eclampsia/eclampsia reported by Grünfeld *et al.* (1980). Stratta *et al.* (1987) reported 17 patients with acute renal failure attributed to pre-eclampsia/eclampsia, of whom five had irreversible renal damage due to renal cortical necrosis and three died. Four of the patients with renal cortical necrosis and all the deaths occurred in the eight patients in whom placental abruption was superimposed on pre-eclampsia/eclampsia. Thus, most patients with acute renal failure due to pre-eclampsia/eclampsia make a complete recovery but there appears to be a high frequency of irreversible renal failure and death in those who also suffer placental abruption.

In common with all patients with severe pre-eclampsia/eclampsia, patients with the HELLP syndrome should receive immediate drug treatment for hypertension and seizures. In pregnant patients urgent delivery usually brings about rapid resolution and has been recommended as routine management (Weinstein 1982; 1985). MacKenna *et al* (1983) advocated an alternative approach in which the use of intravenous magnesium sulphate for seizure control and hydralazine for hypertension combined with intensive maternal and fetal monitoring enabled pregnancy to be prolonged until the fetal lungs were mature. Our patient, in whom eclampsia occurred post partum, was initially treated conventionally with anticonvulsant and antihypertensive agents. On the second day postpartum, in view of persistent thrombocytopenia, we instituted a continuous intravenous infusion of prostacyclin (epoprostenol, PGI_2) which was continued for 5 days until the platelet count returned to normal.

Prostacyclin is a naturally occurring prostaglandin. It is a potent vasodilator and inhibitor of platelet aggregation. Prostacyclin is produced primarily by vascular endothelial cells including those of the maternal and fetal circulations. Thromboxane A_2, the main endogenous antagonist of prostacyclin, is produced mainly by platelets but also in vessel walls and in pregnancy-associated tissues. In normal pregnancy, production of both prostacyclin and thromboxane A_2 is increased and the balance between these prostanoids is believed to be important in the control of the haemodynamic changes of pregnancy. Reduced levels of prostacyclin or reduction in the ratio of prostacyclin to thromboxane A_2 have been demonstrated in numerous studies of maternal and fetal tissues in pre-eclampsia and may be responsible for the vasoconstriction, platelet hyperactivity and endothelial dámage that occur in pre-eclampsia (reviewed by Ylikorkala & Mäkilä 1985; Friedman 1988).

Infusion of synthetic prostacyclin as a treatment for severe pre-eclampsia was first reported by Fidler *et al.* (1980). In that patient, prostacyclin infusion at 8 ng/kg/min was successful in controlling hypertension after conventional treatment had failed, but after 3 days of therapy, delivery by caesarean section at 27 weeks gestation was necessitated by three periods of fetal bradycardia. Mother and baby both survived. Lewis *et al.* (1981) reported a patient with pre-eclampsia in whom prostacyclin infusion at a rate of 4 ng/kg/min improved blood pressure slightly but fetal death occurred unexpectedly at 25 weeks gestation after 4 days of therapy, Belch *et al.* (1985) treated five women with pre-eclampsia with prostacylin infusions at rates of 0·5–6 ng/kg/min for between 5 h and 11 days with improvement in blood pressure and platelet consumption. However, in one patient fetal death occurred at 26 weeks gestation after 11 days of therapy. In this patient, the dose of prostacyclin was limited by the occurrence of severe headache and flushing and adequate control of blood pressure was not achieved. No serious maternal or fetal side-effects were noted in the other four patients. Thus, infusion of prostacyclin may ameliorate hypertension and platelet consumption in pre-eclampsia, probably by improving relative prostacyclin deficiency. The use of prostacyclin in pre-eclampsia has been associated with the occurrence of fetal distress and death but, in the absence of controlled trials, it is not clear whether the incidence of these complications is higher in prostacyclin treated patients than in those managed in other ways. At present, widespread use of prostacyclin in pre-eclampsia cannot be advocated though its use may be justified in cases which are resistant to conventional therapy or in patients in whom severe hypertensive disorders appear post partum.

In summary, our patient suffered from eclampsia, with associated haematological and hepatic abnormalities, and acute renal failure after a normal pregnancy and delivery. Treatment included a continuous intravenous infusion of prostacyclin which appeared to help in blood pressure control and was associated with improvement in the platelet count. There were no serious adverse effects. However, the contribution of prostacyclin therapy to the patient's complete recovery remains uncertain. We can find no previous report of a similar case.

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ADONIS 030654569100101C

Spontaneous variation in fetal pleural effusions. Case report

M. PARKER, D. JAMES

A 34-year-old woman with two normal previous pregnancies was found on routine ultrasound scan at 18 weeks gestation to have a fetus with bilateral pleural effusions. The effusion was much larger on the right side, with a collapsed right lung; the effusion on the left side was discernable as a thin rim of fluid (Figs. 1a and b).

There were two episodes of fetal bradycardia. During one of these episodes there was a suspicion of asynchronization of atrial and ventricular activity. The episodes of bradycardia were shortlived and returned to normal before M-mode assessment could be made. Prolonged fetal heart rate (FHR) monitoring was not recorded at this stage. The FHR was recorded for 15–20 min weekly from 20 weeks until 28 weeks gestation and thereafter for 30–60 min weekly until 35 weeks gestation. The FHR was recorded for 30–36 min daily from 35 weeks gestation until delivery, using a domiciliary fetal monitoring system (James *et al.* 1988). No FHR abnormality was detected during the remainder of the pregnancy using this intermittent observational approach. There was no associated ascites or hydrops. The amniotic fluid volume was normal. The placenta was antero-fundal and appeared normal. There were no other fetal anomalies detectable on detailed ultrasound examination.

After appropriate counselling, a cordocentesis was performed. The fetal karyotype was normal and there was no evidence of anaemia, haemoglobinopathy or viral infection.

In view of the normal results and the presumed diagnosis of chylothorax, the woman was seen again at 20 weeks gestation with a view to draining the right pleural effusion *in utero*. However, at that time there was no longer any ultrasound evidence of a left pleural effusion and the effusion on the right side was much reduced, with the lung re-expanded (Fig. 2). In view of this spontaneous improvement no invasive procedure was undertaken.

Therafter, the fetus was scanned every 4 weeks. The effusions had completely disappeared by 24 weeks (Fig. 3) and the pregnancy progressed satisfactorily until 35 weeks gestation when ultrasound showed that the right pleural effusion had reaccumulated. There was no associated ascites, polyhydramnios or fetal heart rate abnormality. The fetus was appropriately grown by head and abdominal circumference measurements. One week later the effusion was much larger but, again, no other abnormality was detected.

Following discussion between obstetric and neonatal staff, labour was induced at 36 weeks by amniotomy and oxytocin infusion. A female infant weighing 2610 g was born normally following a 4-h labour during which the FHR was monitored continuously. There was no evidence of birth asphyxia and no need for neonatal resuscitation (the Apgar score was 8 at 5 min). Examination revealed no abnormality. Chest X-ray confirmed a right pleural effusion (Fig. 4) but cardiac size and outline were normal. Echocardiography was normal. Continuous electrocardiographic recording of heart rate on the neonatal intensive care unit for 48 h was normal. No treatment of the pleural effusion was considered necessary.

Both mother and baby remained well and were discharged from hospital on the fourth day. The infant was well when reviewed at 4 months

Discussion

Fetal pleural effusions are important because they may indicate an underlying serious problem, such as chromosomal abnormality (Down's or Turner's Syndrome), viral infection or cardiac

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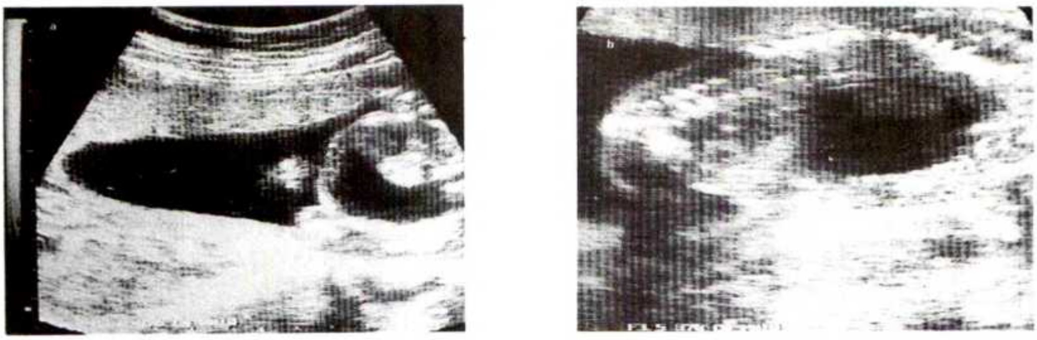

Fig. 1. Ultrasound appearances of the fetal pleural effusions at 18 weeks (see text): (a) Transverse view of fetal chest showing large right pleural effusion. (b) Longitudinal view showing right pleural effusion only and collapsed right lung.

anomaly (with or without arrhythmia) and also they may lead to pulmonary hypoplasia or progress to hydrops fetalis.

Fetal pleural effusions are readily diagnosed by ultrasound. The first reports of detection *in utero* were by Carroll (1977) and Defoort & Thiery (1978) who described fetuses with large pleural effusions and also generalized hydrops fetalis. The first isolated pleural effusion was reported by Thomas & Anderson (1979). Although in our patient the diagnosis was made at 18 weeks gestation, two-thirds of cases are diagnosed during the third trimester (Adams *et al.* 1988). Adams *et al.* (1988) also reported that pleural effusions were commoner in male fetuses (60%), were bilateral in 47% and were associated with polyhydramnios in 53%. Congenital pleural effusions may be associated with non-immune or immune hydrops fetalis, cardiac anomalies with or without arrhythmias, viral infection or chromosome abnormalities, but the commonest cause is congenital chylothorax. The development of pulmonary hypoplasia in association with pleural effusions was first reported by Bovicilli *et al.* (1981) and is a major influence on prognosis.

The pathognomonic sign of a pleural effusion on an ultrasound scan is an echo-free area lying between the lung and the chest wall (Fig. 1). Sonography may also indicate secondary changes including a suspicion of pulmonary hypoplasia, mediastinal shift, hydrops fetalis and polyhydramnios. Detection of pleural effusion *in utero* is important. It is associated with a mortality rate of 15% (Jaffa *et al.* 1985). Prenatal

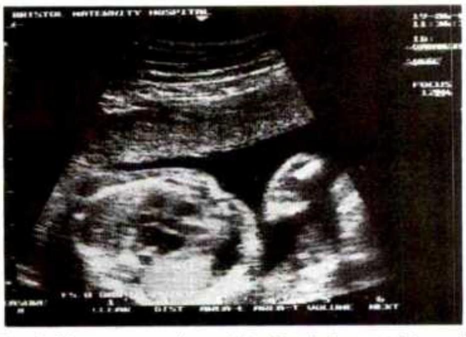

Fig. 2. Transverse view of the fetal chest at 20 weeks showing much reduced right sided pleural effusion.

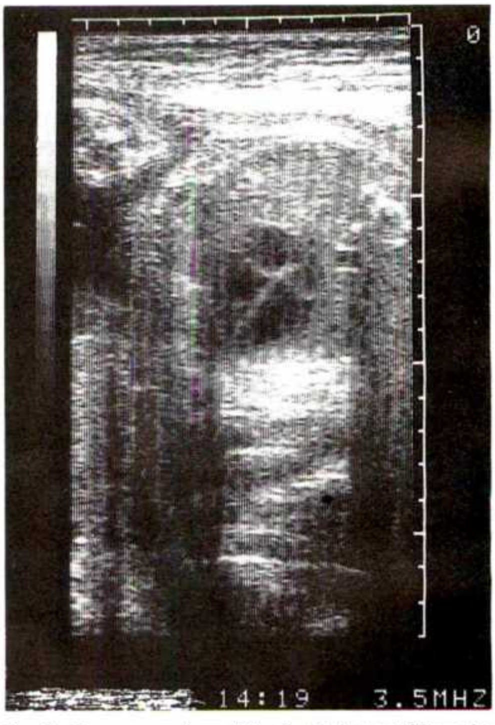

Fig. 3. Transverse view of the fetal chest at 28 weeks with no evidence of a pleural effusion.

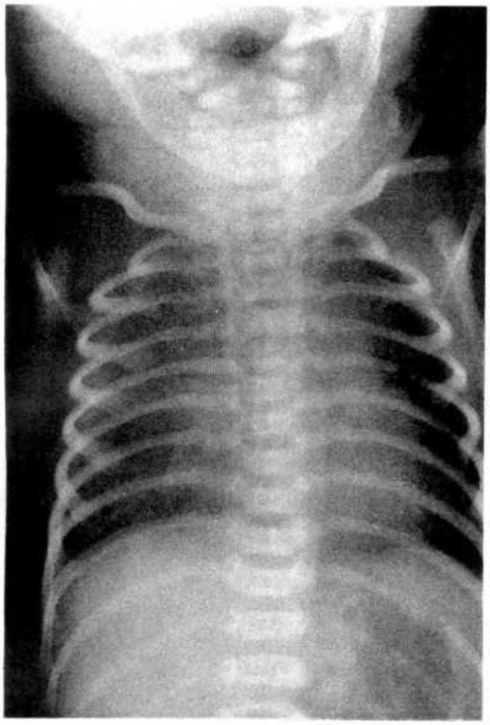

Fig. 4. Supine chest X-ray taken on the first day showing increased opacity of the right lung fields compared with the left and lateral fluid levels consistent with a right sided pleural effusion.

detection allows further investigation of the cause and a rational consideration of *in utero* treatment, the timing and mode of delivery and the arrangements for prompt and appropriate neonatal management.

In our patient the diagnosis of pleural effusions was made at 18 weeks gestation and cardiac anomaly, chromosomal abnormality, viral infection, fetal anaemia and haemoglobinopathy were excluded. One valid criticism of the management is that aspiration of the right sided effusion was not performed at the same time as the cordocentesis at 18 weeks. If chylothorax was the cause then examination of the aspirated fluid would have confirmed this. Having excluded serious underlying causes mentioned above, we had proposed to insert a chest drain *in utero* at 20 weeks to prevent the development of pulmonary hypoplasia or fetal hydrops (Booth *et al.* 1987). However, as the effusions had then disappeared the procedure was not undertaken. We speculate that the effusions were due to either chylothorax, which is known to resolve spontaneously, or a transient fetal cardiac arrhythmia. The reappearance of the right pleural effusion at 35 weeks gestation is more difficult to explain. We are not aware of reports of chylothorax recurring and although there was a suspicion of FHR abnormality initially, there was no evidence of this later in pregnancy despite close fetal surveillance. Admittedly, the FHR monitoring was intermittent and it is possible that a transient arrhythmia was missed. Bradycardia can be a normal feature of fetal development in the first half of pregnancy and of no relevance to the effusions (Pillai & James 1990). Another possible explanation for the fluctuating nature of the pleural effusions is temporary closure of the foramen ovale (W. Holzgreve, personal communication). By 36 weeks delivery and neonatal treatment was considered preferable to *in utero* drainage of the pleural effusion. This case report indicates that pleural effusions can resolve spontaneously with an excellent outcome.

Acknowledgments

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Renal endometriosis treated with a gonadotrophin releasing hormone agonist. Case report

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Case report

A healthy woman had first experienced macroscopic haematuria in 1981 at the age of 25. Initially she had intravenous urography, renal angiography and cystoscopy, all with negative findings. Daily haematuria persisted for 3 years and was more pronounced with physical exercise but not with menstruation. She developed diffuse back-pain of increasing severity.

In 1984 selective angiography of both kidneys revealed a possible tumour in the left kidney. Ultrasound examination showed a 40 mm cystic tumour at the upper pole of the left kidney. This was punctured and cytological examination revealed fragments of glands with cuboidal epithelium. This epithelium was not of renal origin and, as the puncture was performed retroperitoneally, could not have been obtained from the gastrointestinal tract. Blood cells were present inside the glandular fragments and renal endometriosis was suspected. Because of this and because of the discovery of a pelvic tumour, 15 mm in diameter, she was referred to the Department of Obstetric and Gynaecology. At laparotomy an endometriotic cyst was removed from her left ovary. No endometriosis was observed elsewhere in the pelvis or abdomen.

She was treated with the progestogen lynestrenol 5–15 mg/day for 6 months. The dose was increased until she developed amenorrhoea. Macroscopic haematuria ceased but microscopic haematuria persisted. The back-pain was less intense.

Severe back-pain and macroscopic haematuria recurred in October 1984, 4 months after the end of the progestogen therapy. Laparoscopy revealed three separate pelvic endometriotic cysts, but they were each only 1 mm in diameter. Cytological examination of the urine showed no cells suggestive of urinary endometriosis.

The woman was then treated with a GnRH agonist (nafarelin, generic name E-(Na12)-6-GnRH), Syntex, Co) for 11 months. Initially 125 µg was administered daily by nasal inhalation. The patient developed amenorrhoea and plasma oestradiol levels were in the postmenopausal range (60–100 pmol/l). Microscopic haematuria had ceased by 3 weeks and the back-pain by 4 weeks.

Because of intermittent slight uterine bleeding the dose was increased after a month to 250 µg daily and continued for 9 months.

No endometriosis was seen at a post-treatment laparoscopy. Two months after the end of the nafarelin treatment the microscopic haematuria recurred. Computerized tomography showed a cystic 20 mm tumour at the site of the original lesion in the left kidney. A puncture was performed but the cytological examination showed only blood cells and macrophages.

Three months later the patient had macroscopic haematuria daily, together with moderate to severe back-pain. Cystoscopy showed blood originating from the right ureteric opening. The ureter was catheterized and rinsed with saline. Cytological examination showed degenerated cubical epithelial cells that were judged to be endometrial cells affected by hormonal treatment.

Treatment with the GnRH agonist, 250 µg daily was reinstituted. She became clinically and subjectively free of symptoms within one month, and the treatment was continued for 8 months.

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Since then the patient had no urinary tract symptoms and no pain. Post-treatment computerized tomography showed a persistent 20 mm cystic tumour in the left kidney. A further puncture was performed and cytological examination showed only degenerated blood cells. The length of follow-up is now 41 months (February 1990) and there has been no macroscopical or microscopical haematuria.

The patient, became pregnant in June 1988 but, unfortunately, had a miscarriage 3 months later.

Discussion

Renal endometriosis is considered to be a rare disease and only 11 patients have been reported (Rosdy *et al.* 1979). In two of these the diagnosis was found unexpectedly at post mortem examination. In all the others the diagnosis was made after nephrectomy. In only two women had there been symptoms which were clearly worse at menstruation. Common clinical features were macroscopic haematuria, back-pain and suspicion of a renal tumour on X-ray examination. The symptoms were not usually related to the menstrual cycle (Rosdy *et al* 1979).

The clinical features of our patient correlate well with previous case reports.

We used ultrasound-guided puncture of the kidney and catheterization of the ureter during haematuria as diagnostic methods. Cytology could not definitively confirm endometriosis but, in combination with the clinical history, the finding of pelvic endometriosis and the response to treatment, the diagnosis seems clear. Intraluminal ureteral endometriosis is more commonly reported than renal endometriosis. Endometriosis should always be considered when there is haematuria and back-pain in fertile women, after nephrolithiasis, infection and malignant disease have been excluded.

Progestogens are generally accepted as treatment for endometriosis but were unsuccessful in our patient despite a large dose and 6 months of treatment. However, subsequent treatment with a GnRH agonist to reduce oestradiol secretion led to rapid control of symptoms. Two treatment periods of 11 and 8 months, respectively, were necessary before she was cured. The recommended treatment for endometriosis with GnRH is 400 μg daily. It is, however, usual to treat extra-genital endometriosis with a higher dosage. Consequently the successful treatment with such a low dose as 250 μg is encouraging. No subjective side effects were reported during the GnRH agonist treatment, except for amenorrhea. There were no hypoestrogenic symptoms such as hot flushes or dyspareunia, probably because of the low dose used. The treatment of endometriosis with GnRH agonists has recently been reported as effective for pelvic endometriosis (Editorial, 1986).

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Epidural analgesia for labour in Takayasu's arteritis. Case report

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Case report

A 23-year-old primigravida was referred for antenatal care at 14 weeks gestation. Takayasu's arteritis had been diagnosed 2 years previously and angiography at that time had shown total occlusion of the right subclavian and brachial arteries with distal occlusion of the left subclavian artery; electrocardiography (ECG) and fundoscopy were normal. Initially the pregnancy progressed normally but from 30 weeks gestation onwards the patient developed hypertension and proteinuria. At 36 weeks, she was admitted for induction of labour. On admission her heart rate was 96/min. No pulses were palpable in her upper limbs. The blood pressure was measured using a thigh cuff and a Critikon 'Dinamap' recorder, readings were similar at 160/85 mmHg in both legs. She was reviewed by a cardiologist who found no evidence of cardiac decompensation and confirmed that her ECG was normal. Urea and electrolytes were normal but a full blood count revealed a microcytic anaemia (Hb 8·0 g/dl); the platelet count was normal. Amoxycillin with clavulanic acid ('Augmentin') was prescribed prophylactically.

An epidural catheter was inserted at the third lumbar interspace. Analgesia was established with 10 ml of 0·375% bupivacaine in divided doses, in right and left lateral positions. Pulse rate and blood pressure were recorded every 5 min for 30 min after each top up.

Labour was stimulated with intravenous oxytocin. The fetal heart rate and intrauterine pressure were recorded continuously.

Analgesia was maintained with a cumulative total of 127 mg bupivacaine over a 9-h period. There was no evidence of fetal distress during labour. Full cervical dilatation was reached after 8 h in labour and she was delivered with Haig-Ferguson forceps following an epidural top-up of 8 ml 0·5% bupivacaine which produced a sensory block to the sixth thoracic dermatome level. Her blood pressure rose to 200/92 mmHg just before this top-up but was otherwise reasonably controlled (systolic 120–180, diastolic 80–100 mmHg) throughout labour. Five units of oxytocin were given intramuscularly with the birth of the anterior shoulder. Epidural analgesia was discontinued after delivery.

A live male infant weighing 2230 g was born with Apgar scores of 9 at 1 min and 10 at 5 min. He developed mild respiratory distress syndrome but recovered quickly. After delivery, the mother's blood pressure increased to 190/110 mmHg and a total of 80 mg intravenous hydralazine was given over a 48 h period. Six days after delivery the patient was discharged from hospital on no medication. She was well at follow up 6 weeks later, and her blood pressure was at the pre-pregnancy level.

Discussion

Takayasu's arteritis is a chronic occlusive arteritis of the aorta and its branches. Over 85% of affected patients are young women, the average age at the time of diagnosis being 30 years (Ishiwaka 1978). The effects of pregnancy, labour and delivery on the course of Takayasu's arteritis have been described by Ishiwaka & Matsura (1982) and Wong *et al.* (1983).

The commonest complications in Takayasu's

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arteritis, related to hypertension and cardiac failure, are most likely to occur in the perinatal period (Wong *et al.* 1983).

Intracerebral haemorrhage is a recognised complication (Ishiwaka 1982) and sudden increases in blood pressure must be avoided. Epidural analgesia can provide relief throughout labour and for controlled forceps delivery, and it can reduce the level of hypertension. However, hypotension is also particularly hazardous in Takayasu's arteritis because of the marked variations in regional blood flow which may compromise organ perfusion. Careful management of the epidural is essential. The need for vascular stability in our patient precluded the use of ergometrine because of its adverse cardiovascular effects (Johnstone 1972). Synthetic oxytocin (Syntocinon) was considered the oxytocic of choice.

The use of a thigh cuff with a Critikon 'Dinamap' recorder allowed frequent measurements of blood pressure in our patient but invasive monitoring by arterial cannulation may also be considered. Thorburn & James (1986) found that epidural analgesia was of value for control of pain and blood pressure when used post-operatively. They recommended insertion of a Swan Ganz catheter in all patients, but in our patient, in the absence of cardiac failure, we did not consider the risks of pulmonary artery catheterisation to be justified.

Continuous epidural infusion of bupivacaine might provide greater haemodynamic stability, although this cannot be assured since the need for bolus top-ups remains (Clark 1982; Abboud *et al.* 1984; Gaylard *et al.* 1987). We judged it safest to use the methods most familiar to all concerned.

Acknowledgments

We would like to thank Dr N. Patel, consultant obstetrician, for allowing us to report his patient.

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Acromegaloid bone changes in severe polycystic ovarian disease: an effect of hyperinsulinaemia? Case report

ROBERT FOX, PETER G. WARDLE, LEO CLARKE, MICHAEL G. R. HULL

Case report

A 33-year-old woman presented to the reproductive medicine clinic with amenorrhoea of 14 years' duration together with progressively worsening hirsutism for 8 years, temporal hair loss for 4 years and infertility for 2 years. She had previously failed to respond to clomiphene citrate but was currently receiving no therapy. Her mother had developed diabetes mellitus in late adult life.

On examination she was markedly overweight (body mass index 47·2 kg/m) with severe hirsutism and hair loss over the vertex and temporal areas. She had broad hands with thickened skin and acanthosis nigricans of the inner thigh. Her blood pressure was mildly elevated (140/90 mmHg). Abdominal and vaginal examination revealed a pelvic mass.

A 13-cm multiloculated cystic lesion arising from the left side of the pelvis was seen on ultrasound scan. The ovaries were not seen separately and there was no ascites. An endocrine profile showed raised serum concentrations of luteinizing hormone (LH) (19 U/l), total testosterone (6·2 nmol/l) and dehydroepiandrosterone-sulphate (12·3 umol/l), but normal levels of FSH (3·4 U/l), prolactin (99 mU/l) and free thyroxine (13·9 pmol/l). She had an elevated fasting insulin concentration (37 U/l; normal range <15 U/l) but normal blood glucose concentrations, both fasting (4·4 mmol/l) and 60 min after a 75 gm oral glucose load (7·6 mmol/l). A 24-h urine collection showed normal excretion rates of cortisol (76 nmol/24 h; normal range <290 nmol/24 h) and cortisol precursors (0·4 mmol/M creatinine; normal range 0·2–0·6 mmol/M creatinine). Serum oestradiol concentrations (190 pmol/l) were unremarkable but oestrogen deficiency was demonstrated on two occasions by a negative response to progestogen challenge.

Radiological examination of the chest was normal but hand X-rays, undertaken because of their unusual configuration, showed tufting of the distal phalanges suggestive of acromegaly (Fig. 1). Moderate prognathism of the mandible was noted on skull X-ray but there was no thickening of the calvarium or hypertrophy of the frontal sinuses. The pituitary fossa was normal.

Growth hormone (GH) was measured in serum following a 10-h overnight fast and 30, 60 and 120 min after a 75 gm glucose load. The basal and post-glucose GH concentrations were all below the limit of sensitivity of the assay (1 mU/l). Serum insulin-like growth factor-1 (IGF-1) concentration was normal (43·0 nmol/l; normal range 11·6–48·4 nmol/l).

At laparotomy a cystic mass was found to be arising from the left ovary. Both ovaries were enlarged with multiple small subcapsular cysts. The cystic mass was removed and a deep wedge biopsy (including the hilus) was taken from each ovary. On microscopy the tumour was found to be a multiloculated benign serous cystadenoma. The ovarian biopsies contained numerous small follicular cysts together with stromal hyperplasia but no evidence of an androgen-secreting tumour. Her testosterone levels fell dramatically after the wedge resection (2·3 nmol/l) but she failed to ovulate spontaneously and remained resistant to clomiphene citrate. Conception was achieved in the first cycle of exogenous gonadotrophin therapy. Diabetes mellitus developed

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at 20 weeks gestation and the glucose intolerance persists 6 months after delivery.

Discussion

Amenorrhoea, hyperandrogenism and acanthosis nigricans are well recognised features of both severe polycystic ovarian disease (PCOD) and GH excess (Bayliss 1978; Barbieri & Ryan 1983), but this is only the second report of clinical signs of acromegaly in association with PCOD. Flier *et al.* (1980) described a woman with virilization associated with severe insulin resistance and acral hypertrophy. Our patient's basal and post-glucose GH concentrations were not elevated, excluding GH excess as the cause of the radiological findings. Indeed GH was undetectable in her fasting sample, consistent with the finding of GH hyposecretion in women with PCOD (Urdl 1988).

Mims (1978) described 11 women with clinical and radiological appearances of acromegaly and low GH concentrations, but none had features suggestive of PCOD. He termed the condition acromegaloidism and speculated that the somatic changes were the result of increased synthesis of somatomedin-C (IGF-1), occurring independently of GH. Locally produced IGF-1 is thought to mediate the action of GH on physiological bone growth (Froesch *et al.* 1985) and evidence that serum concentrations of IGF-1 are raised in parallel with GH in acromegaly (Barkan *et al.* 1988) appears to indicate that the peptide is also responsible for the disordered bone growth. Mims (1978) did not measure IGF-1 levels in his patients, and our patient's serum IGF-1 concentration lay within the normal range. The possibility that these effects are mediated by IGF-1 itself cannot be entirely discounted as serum concentrations of the lower molecular weight IGF-1 binding protein are reduced in PCOD (Suikkari *et al.* 1989) and the unbound (active) fraction of IGF-1 may be increased (Pekonen *et al.* 1989).

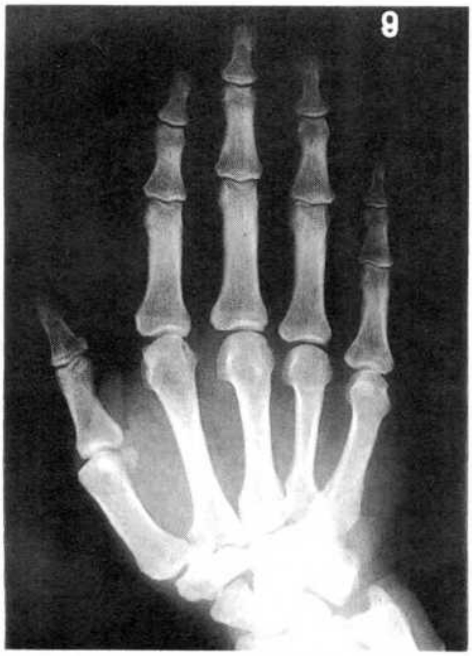

Fig. 1. X-ray of patient's right-hand showing tufting from terminal phalanges.

A more plausible candidate for the mediation of these effects is insulin. In common with many women with PCOD, our patient had clear evidence of fasting hyperinsulinaemia (Chang *et al.* 1983) and an inherited prediposition to non-insulin-dependent diabetes mellitus (Gjonnaess 1989; Fox 1989). Interestingly, 8 of the 11 acromegaloid women described by Mims (1978) also had occult glucose intolerance. As a result of close structural homology, insulin and IGF-1 are able to bind each other's receptor (Froesch & Zapf 1985) and the increased LH-dependent androgen production characteristic of PCOD is thought to be induced, in part, by insulin (Barbieri *et al.* 1984) acting upon the IGF-1 receptors on thecal tissues (Poretsky & Kalin 1987). It seems likely, therefore, that the bony changes seen in this patient were also the result of abnormally high concentrations of insulin acting upon IGF-1 receptors in bone.

Despite evidence of overgrowth of cortical bone, osteoporosis is a well recognised complication of acromegaly and kyphosis is a frequent finding in advanced disease (Steinbach *et al.* 1959). Although there is no evidence of bone loss in oligo-amenorrhoeic women with mild hyperandrogenaemia (Dixon *et al.* 1989), further study of bone mineral density is warranted in patients with severe PCOD particularly as this subgroup of patients are more likely to be oestrogen deficient (Hull 1987).

The acromegaloid bone changes in this patient appear to be adequately explained by the abnormal insulin state associated with her ovarian disorder. As patients with classical acromegaly may also present with hirsutism, obesity and amenorrhoea, the possibility of GH excess should not be disregarded in patients with the polycystic ovary syndrome. On the other hand, the absence of excessive GH secretion in any patient with clinical features of acromegaly should alert the clinician to an increased risk of diabetes mellitus, particularly during pregnancy.

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ADONIS 030654569100105U

SHORT COMMUNICATIONS

Intrauterine infection and miscarriage following trans-abdominal chorionic villus sampling. Case report

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A 36-year-old woman requested chorionic villus sampling in view of her age. As she had previously had genital herpes she requested that the procedure be carried out by the trans-abdominal route. Ultrasound scan confirmed the presence of a viable pregnancy at 9 weeks gestation with a posteriorly implanted chorion. Chorionic villus sampling was performed using the double needle technique and 10 mg of tissue were obtained without difficulty. Following the procedure the woman felt faint and vomited but was allowed home a few hours later.

She was readmitted 12 h later to the gynaecology ward with malaise, headache, pelvic pain and bloodstained watery discharge. Her abdomen was soft with no evidence of peritonism. The uterus was slightly tender.

Over the next few hours her condition deteriorated. She became hypotensive and developed a tachycardia. Ultrasound scan revealed a collapsed amniotic sac. No fetal heart movements were seen. A diagnosis of infected miscarriage was made. Evacuation of the uterus was carried out under antibiotic cover using intravenous cephalexin and intravenous metronidazole. Thereafter she made an uneventful recovery and was discharged home after 48 h. Maternal blood culture revealed a mixed growth of *Clostridium perfringens* and *Streptococcus faecalis* and these organisms were also cultured from the products of conception.

Discussion

Chorionic villus sampling is now becoming more widely available for the prenatal diagnosis of chromosomal and genetic disorders. Trans-abdominal sampling may be preferred because of the potential risk of transfer of organisms by the catheter through the cervix when the trans-cervical technique is employed (Garden *et al.* 1985). Infected miscarriage after trans-cervical chorionic villus sampling has been reported (Barela *et al.* 1986).

Intrauterine infection and miscarriage have not been reported previously following trans-abdominal chorionic villus sampling. Skin contamination is unlikely in this case because of the organisms involved. Infection due to inadvertently piercing the bowel at the time of the procedure is a possible cause. However, the speed of onset of symptoms and the absence of abdominal signs before the administration of antibiotics need to be explained. In addition, careful ultrasound scanning before and during the procedure failed to demonstrate loops of bowel. The possibility that infection was already present in the chorion before the procedure also needs to be considered.

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Serum level of secretory endometrial protein PP-14 in intact ectopic pregnancy

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In a study of secretory endometrial protein PP–14 in early pregnancy we observed two women with very low serum concentrations, both of whom had ectopic pregnancies. Because a low serum value would be expected with a failed pregnancy, we prospectively studied women in whom an ectopic pregnancy with fetal heart activity was found incidentally at ultrasound. We have now seen two such pregnancies, at 49 and 52 days gestation, as judged from the crown-rump length (Pedersen, 1982), and both women had low serum PP–14 concentrations.

Subjects, methods and results

Our reference range for PP–14 levels at 6–7 weeks gestation is based upon a single serum PP–14 determination in each of 20 pregnant women. Gestational age was confirmed by ultrasound (range 45–56 days, median 50 days) and informed consent was given to have a blood sample taken. PP–14 was determined by a highly specific radioimmunoassay (Byrjalsen *et al.* 1989). The median PP–14 value in the control sera was 1·35 mg/l (range 0·71–3·54 mg/l, 5th centile 0·72 mg/l). Serum PP–14 concentrations in the two ectopic pregnancies were 0·45 and 0·22 mg/l, respectively, far below the 5th centile ($P<0{\cdot}05$, rank sum test).

Discussion

PP–14 is synthesized in the decidua (Julkunen 1986). We do not know why the serum concentration of PP–14 is low in ectopic pregnancy. A possible explanation is that as blood is drained from the intervillous space of the placenta it passes in close contact with the decidua via blood sinuses (Hamilton *et al.* 1962), whereas in a tubal pregnancy the blood will be in contact with the poorly decidualized mucosa of the fallopian tube. The value of our observation is that it might permit the diagnosis of ectopic pregnancy before symptoms, or any serious threat to the pregnant woman, and early enough to allow for a conservative treatment to preserve the fallopian tube (Vermesh 1989).

One could speculate that if PP–14 levels in intact ectopic pregnancy were below the 5th centile (particularly before 7 weeks gestation, when viability is difficult or impossible to prove), and given that the frequency of ectopic pregnancy is 1% (Weström *et al.* 1981), then a PP–14 test in early pregnancy could identify 5% of the pregnant women, who would then have a risk of having an ectopic pregnancy of one in five or 20%. In an at-risk population with previous pelvic inflammation or tubal surgery the figures could be still more favourable. One might even envisage a dual pregnancy test: an hCG assay to prove pregnancy and a PP–14 assay to exclude an ectopic pregnancy.

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ADONIS 030654569100107M

CORRESPONDENCE

Randomized comparison of routine vs highly selective use of Doppler ultrasound and biophysical scoring to investigate high risk pregnancies

Dear Sir,

The article by Tyrell *et al.* [*Br J Obstet Gynaecol* (1990) **97**, 909–916] offers some conclusions which seem difficult to sustain. Since the two groups arising from the randomization of 500 high risk pregnancies received different standards of antenatal care any difference in outcome between them could not be ascribed to a particular factor, be it the use of Doppler, biophysical scoring or just a visit to the hospital. The fact that this is not a randomized *controlled* trial underlines its weakness and makes interpretation more surmise than science. The statement that 'we now offer Doppler investigations to all high risk pregnancies . . .' implies that the study has demonstrated the efficacy of this method of investigation something which does not seem, to us, to be justifiable based on the data presented.

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Authors' reply

Dear Sir,

We do not believe that the two groups of randomised high risk pregnancies received different standards of antenatal care. The only difference in antenatal care between the two groups was that the study group had the routine use of Doppler and biophysical scoring. There is no evidence that, other than this aspect, there was any different standard of obstetric care applied to the patient. There was no difference in the rate of admission to the antenatal ward, the duration of stay on the antenatal ward, induction of labour or elective caesarean section between groups. The whole point of the trial was to look at the differences resulting from the routine use of Doppler and biophysical score, in addition to the already high standards of antenatal care offered. We accept that the trial was not controlled, however, data that were not published at the request of the editor, pointed out that there was no difference between groups with regard to maternal age, parity or number of cigarettes smoked per day at the time of booking. There was also no difference in social class between the two groups. Therefore, although not strictly controlled, we had no evidence that the two groups were in any way significantly different. We were at pains to demonstrate that this study does not mean that the routine use of Doppler ultrasound in high risk pregnancy has a proven place in obstetric practice. To us the most important finding of the study was that there appeared to be no adverse effect on patient care and obstetric intervention as a result of the introduction of this technique into routine practice. Clearly to demonstrate the efficacy of Doppler with or without a biophysical score as a routine in such pregnancies would require either a much larger study or many other similar sized studies compared together using a meta-analysis. It does so happen, however, that we believe that we can justify the use of this technology in high risk pregnancy, although we accept that not everyone else will hold the same view.

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ADONIS 030654569100108Z

Uterine rupture in midtrimester abortion. A complication of gemeprost vaginal pessaries and oxytocin. Case report

Dear Sir,

We were interested to read the article by Wiener & Evans [*Br J Obstet Gynaecol* (1990) **97**, 1061-1062].

We reviewed 1392 midtrimester abortions carried out at the Simpson Memorial Maternity Pavilion from 1 April 1984 to 31 December 1990, when gemeprost pessaries were first used to terminate midtrimester pregnancies. Overall 904 pregnancies (between 12 and 22 weeks gestation) were terminated using the regimen described by Cameron *et al.* (1987), 209 pregnancies were terminated using intra-amniotic prostaglandin E_2 and urea, 275 were terminated with extra-amniotic prostaglandin E_2 and four were terminated with intra-amniotic urea together with gemeprost pessaries. In this consecutive series of 904 midtrimester pregnancies that were terminated with gemeprost, 50 women had pretreatment with mifepristone (Rodger *et al.* 1990).

Of the 904 pregnancies terminated with gemeprost pessaries 158 (17%) required more than five pessaries because abortion had not occurred after 24 h and 37 (4%) failed to abort after a further course of five pessaries. Of the 37 patients who failed to abort after a further course of five pessaries 29 were given an intravenous infusion of oxytocin in incremental dosage to a maximum of 111 mU/min, Four failed to abort following administration of oxytocin, two of these pregnancies were terminated by dilatation and evacuation and the other two with extra-amniotic prostaglandin E_2. In the remaining eight women who failed to abort after 10 pessaries, six had their pregnancies 'electively' terminated using extra-amniotic prostaglandin E_2, one had a dilatation and evacuation and one pregnancy was terminated with intra-amniotic prostaglandin E_2 and urea.

The cumulative abortion rates after 96 h were 99% for gemeprost pessaries (with intravenous oxytocin when necessary), 87% for intra-amniotic prostaglandin E_2 with urea and 99% for extra-amniotic prostaglandin E_2.

In our large series of midtrimester abortions using gemeprost, there was not a single uterine rupture and we would agree with the authors that this complication is rare. In our experience, the use of gemeprost pessaries for midtrimester termination is safe, effective, non-invasive and simple.

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ADONIS 030654569100109E

The effects of hospitalization for rest on fetal growth, neonatal morbidity and length of gestation in twin pregnancy

Dear Sir,

I have been interested to read the article by Crowther *et al.* [*Br J Obstet Gynaecol* (1990) **97**, 872-877]. Their findings of an increased birthweight following rest in hospital in twin pregnancies is very interesting but not surprising.

In a study of Ethiopian women with low nutritional intake, Tafari *et al.* (1980) found that the birthweight depended on the level of the physical activity during the pregnancy. Pregnant women whose physical activity was judged to be low, had significantly heavier babies (mean 3270, SD 368 g) than those who engaged in hard physical work (mean 3060, SD 355 g).

The effect of physical activity on birthweight has been confirmed in many studies from developing countries, where a significant seasonal variation of the birthweight can be observed, reflecting the seasonal workload variations.

There can be little doubt that pregnant women who are not in hospital in Zimbabwe have to work harder than pregnant women in Europe. It would be surprising if the results of the study from Harare could be reproduced in Europe.

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BOOK REVIEWS

Legal Principles and Practice in Obstetrics and Gynecology Vol. 1 edited by Max Borten & Emanuel A. Friedman, Year Book Medical Publishers, Inc., Chicago, London, Boca Raton, 1989, 338 pages, with figures and tables, £38.50

Obstetrics and Gynaecology has become a high risk specialty. Indeed, in the USA, about three-quarters of all obstetricians have been, or are being sued.

This book reports the proceedings of a conference of lawyers and doctors held under the auspices of the Harvard Department of Continuing Education and the Beth Israel Hospital. The discussions and interchange are also included There are 15 sections. Many of the chapters are descriptions of the major areas of risk in the specialty including chapters on fetal distress, breech delivery, shoulder dystocia, ureteral injury and bladder damage. The second chapter on the current status of medical malpractice analyzes the present state of practice in the USA and relies on the data provided by ACOG. These figures show that in 1987, 27% of obstetricians dropped high risk obstetrics and, each year, 12% discontinue obstetric practice altogether. Of physicians between 35 and 44 years of age, 23% reported in 1987 that they had given up practice and over one-third of all obstetricians between 45 and 54 years of age had left practice. It has also had a significant impact on gynaecological surgery, with an increasing tendency to conservation and increased numbers of investigations.

The chapters on individual complications are probably of more interest to the lawyers but they have an all too familiar ring about them. What is depressing is that, even in a book like this, some of the medical participants make the sort of dogmatic statements from which lawyers draw their ammunition and which simply cannot be justified clinically. The law assumes a degree of certainty that we would like to provide but which, in reality, we are incapable of meeting. There is an interesting presentation about the need to preserve the rights of patients against the conspiracy of insurance companies to undermine the credibility of plaintiffs by making strong arguments about the effects of litigation on the profession.

The one thing that is missing from the book is any real statement about the psychological impact of court proceedings on both plaintiffs and defendants. It may be that, in due course, the profession will simply accept litigation as a way of life, but there can be no doubt that litigation has already affected the patient/doctor relationship, and almost invariably to the detriment of the patient.

The final section examines possible ways of resolving these problems and it is here that the book is least satisfactory. In a way, risk management seems to be the final capitulation. There will be arguments that the legal system is different in the USA but there are great similarities in the nature of claims and the pattern of development that is occurring in the UK. The book makes depressing reading but it should be read by all practitioners of obstetrics and gynaecology and all those intending to practice this specialty. It lays out the facts and some of the possible options. It is certain that all attendants on the birth process, both obstetricians and midwives, are in jeopardy and that those who will suffer most in the long run are pregnant women.

E. M. Symonds

Ovarian Cancer: Biological and Therapeutic Challenges edited by F. Sharp, W. P. Mason & R. E. Leake. Chapman & Hall Ltd, London, 1990, 480 pages, with figures and tables, £65.00

This book consists of both the edited papers and the discussions given by experts from around the world at the second Helene Harris Memorial Trust, Biennial International Forum, held in 1989 on the latest developments in ovarian cancer. Many aspects relevant to ovarian cancer were covered, such as pathology, clinical management, molecular biology and genetics. The wide variety of expertise present at this meeting enabled both cross fertilization of ideas between clinicians and scientists and the emergence of new ideas and agreements for national and international co-operation.

The book is divided into six parts, each covering a session held at the meeting. Part I was concerned with genetics, in particular, with patients with a family history of ovarian cancer, a group which accounts for 1% of all ovarian cancers. Patients with 2 or more relatives with ovarian carcinoma have a 3 fold increase of developing this malignancy, and more research into this group might identify genetic mechanisms, which could lead to a better understanding of this disease. In addition, these families could act as models for cancer screening techniques.

The increasing importance of scientific research into the basic biology of ovarian cancer was recognized. Two sessions were devoted to this topic, commencing with a paper by Sir Walter Bodmer on the role of both dominant and recessive oncogenes in cancer. Studies at the DNA level need to be expanded to provide explanations for the malignant transformation of ovarian cells, the course of the disease, its response to treatment and to help to develop more effective therapies.

Other topics covered in the biological sessions were wide ranging, and include an excellent review of cytokine therapy. Possibly of great potential value are the flow cytometry studies which were presented; one showed c. myc. to be a useful tumour marker in serous papillary ovarian carcinoma and another that flow cytometry can be used to study drug resistance in populations of individual ovarian cancer cells. The fourth session was concerned with the early detection and screening of ovarian cancer. The necessity to refer women with pelvic masses and raised tumour markers, particularly CA. 125 to oncological experts for surgery was emphasized. Although current screening techniques using vaginal ultrasound and tumour markers are useful, unfortunately, at the present time there is no evidence that any individual or combination of tests available, achieves the specificity and sensitivity required to screen the general population for early stage ovarian cancer.

Potential advances in treating ovarian carcinoma were discussed. Meta-analysis suggests that cisplatin improves median survival in advanced ovarian cancer but that dose intensity is important in terms of response and survival. The use of new drugs, such as SH3 antagonists for treating chemotherapy induced vomiting, WR2721 to prevent cisplatin induced renal and neurotoxicity, and the haemopoeitic colony stimulating factors, will all allow higher doses of cisplatin to be used in the future. Other experimental approaches, such as intraperitoneal chemotherapy to treat minimal residual disease remain undetermined. Similarly, the diagnostic and therapeutic potential value of radioactively labelled monoclonal antibodies has been recognized but multiple problems still exist in their clinical application.

The final session covered surgical aspects of ovarian cancer, with primary optimal debulking remaining the main goal. Neither interval debulking nor adequate debulking in the presence of large primary tumour, ascites of metastatic disease, have shown any survival advantage. Centres in Italy, Austria and Japan who carry out lymphadenectomy have all shown a high prevalence of pelvic lymph node involvement. This probably occurs by direct spread. Although pelvic and para-aortic lymphadenectomy was associated with significantly improved 5-year survival in women with Stage 3 disease in one study, the influence of lymphadenectomy on survival remains unclear.

Overall this book is an excellent resumé of current research, both clinical and scientific, in the battle to understand and treat ovarian cancer. The work is well presented, referenced and edited and the contents are of a uniformly high standard. I strongly recommend this book to those gynaecologists with an interest in ovarian cancer, and to doctors wishing to pursue research into this malignancy. Those in training would also find this a most stimulating book.

H. Lambert

Chemotherapy of Gynaecologic Cancer, 2nd Edition, edited by Gunter Deppe. Wiley Liss, New York, 1990, 165 pages with figures and tables, $165

This book, now in its second edition, is for gynaecologists, and cancer specialists who use cytotoxic drugs to treat the whole range of gynaecological cancers. As this is by American authors the management of breast cancer is also included.

The book can be roughly divided into three parts. The first three chapters cover the principles of cancer chemotherapy, starting with basic cell biology. The pharmacology of cytoxic drugs is dealt with in some detail and includes the development of new drugs, the classification of cytotoxic drugs and their individual therapeutic efficacy in gynaecological cancer. A whole chapter is devoted to the management of adverse effects of chemotherapy. The third chapter is written by a statistician, and covers the design, analysis and interpretation of chemotherapy trials. This is an excellent review of the complexity of designing effective clinical trials and also emphasizes the dangers of drawing conclusions from the interpretation of small non-randomized studies.

The major part of the book consists of individual chapters on the use of chemotherapy at each gynaecological site—vulva, vagina, cervix, endometrium, ovary, fallopian tube. There is also a chapter on the chemotherapeutic management of gestational trophoblastic tumours. These chapters are review articles which consider both the activity of single agents and the results of various combinations of chemotherapy. Hormonal treatments and innovative therapies, such as multi-modal approaches are also covered. Some chapters reflect the paucity of information at present available, such as, on the chemotherapy of vulva and vaginal malignancies, fallopian tube neoplasms, sarcomas and lymphomas, where most of the studies reviewed are small, non-randomized, and, therefore, are not significant. Randomized clinical trials for carcinoma of the cervix and endometrium are also infrequent, giving little firm evidence of the value of chemotherapy, beyond palliation, for these tumours. In contrast, epithelial carcinoma of the ovary has been the subject of many studies and the conclusion is that multi-agent cisplatin based chemotherapy is the most effective. Two further chapters on ovarian cancer cover germ cell tumours and malignant ovarian stromal tumours. In the final chapters, special subjects, such as chemotherapy for cancer in pregnancy, tumour markers and steroid recepters in endometrial cancer, are discussed and there are brief accounts of experimental approaches in immunotherapy, DNA analysis of tumours and the use of monoclonal antibodies.

Overall, there are good and poor aspects to this book. The initial chapters give a good introduction to chemotherapy and in particular to the design and interpretation of clinical trials. In contrast, the review chapters are either so comprehensively referenced that the information is difficult to absorb or their content, as for the uncommon tumours, is of little practical use. However, this book has some value for gynaecologists as it provides an overview of chemotherapy of gynaecological cancers. It is also a good source of references. This book is probably more for a library in view of its high cost.

H. Lambert

A Colour Atlas of Life Before Birth, Normal Fetal Development, by Marjorie J. England. Wolfe Medical Publications Ltd, London 1990, 216 fully illustrated with colour plates. Hardback £37.00, paperback £14.95

When Marjorie England's atlas first appeared in 1983 it gained instant acclaim as an invaluable aid to the study of human prenatal development. The value of the work lies in the use of high quality coloured photographs of whole and dissected specimens throughout, as well as selected radiographs and photomicrographs, rather than the line drawings used in other texts on human development. Copies of this book must be in daily use throughout the world in departments of anatomy, obstetrics, nursing and midwifery schools—and even in pathology departments. My own copy is regularly consulted to aid in assessment of normality of development in small or incomplete fetuses.

The question to be asked of the new reduced-size soft cover edition is whether it represents an adequate alternative to the familiar hard cover version.

The content and layout are identical with no additions or subtractions. Thus, the smaller page size inevitably results in a reduction of print size and some loss of clarity. This is likely to prove more of a hindrance to the presbyopic middle-aged reader rather than the young and impecunious, who may be the most likely purchasers. Similarly the figures in a reduced format are less clear. Additionally, in comparing the reduced-size version with the original, I found that the colour of many of the plates seemed to be of less quality with resultant loss of detail. The information is the same but just a little harder to extract.

At less than half the price of the hard-backed edition the reduced-size verion should certainly find a ready market where price, or ease of transport, are major considerations. The hard cover version is preferable for classroom teaching.

J. S. Wigglesworth

Early Pregnancy Failure (Clinical Obstetrics & Gynaecology) edited by H. J. Huisjes & T. Lind. Churchill Livingstone, Edinburgh, 1990, 278 pages, with figures and tables, £45.00

The latest volume in that splendid Churchill Livingstone series Clinical Obstetrics and Gynaecology, Early Pregnancy Failure certainly lives up to the standards of excellence set by previous publications.

Edited by Huisjes & Lind, two leading researchers in the field, like many multi-author books, the work, when read as a whole, reveals the need for greater editorial direction and blue pencil. Needless interchapter repetition could have been avoided. The contents could have been arranged in a more logical sequence, for example, epidemiology at the beginning rather than at the end. A stronger introduction could have emphasized the difficulties of investigation and treatment in this area, rather than allowing this most important aspect of early pregnancy failure to run throughout the majority of chapters. But such attempts at homogeneity can emasculate. When each chapter is read independently as a monograph, practically no criticisms can be levelled at the work. All potential causes of pregnancy loss are dealt with in an informative, well referenced, readable manner and each chapter ends in an excellent summary.

In particular, clinicians will find the articles on genetics, morphology and psychology helpful. In contrast, the reader has difficulty in deducing the correct way to manage clinical problems, but this is a reflection of the honesty with which the chapters are written. In truth the incidence of miscarriage is unknown, individual cases are difficult to classify by cause, the next pregnancy is a new event, with no guarantee that the happenings in it will be related to past events, so that there is doubt even about the results of placebo controlled studies of therapy. At £45.00 this book is not cheap but the comprehensive nature of each chapter, the references and the index makes it a work of reference that would be a cost effective purchase to all concerned in obstetrics.

Robert F. Harrison

Kistner's Gynecology. Principles and Practice. Fifth edition edited by Kenneth J. Ryan, Ross Berkowitz & Robert L. Barbieri. Year Book Medical Publishers, Inc., Chicago, London, Boca Raton, 1990, 750 pages with figures and tables, £59.00

The 5th edition of this excellent textbook, like the previous four editions which have stretched over the past quarter century provides a state of the art account for the student of gynaecology, both undergraduate and postgraduate.

The layout of the contents differs from most other standard texts in that each organ is dealt with as a separate entity. Starting with the basic sciences of embryology, anatomy and physiology, the reader is then led naturally onto the pathological processes affecting each organ. In addition, there are separate chapters dealing with various landmarks in a woman's life, including paediatric gynaecology, menstrual cycle, adolescent gynaecology, control of conception and the menopause while others deal with specific gynaecological complaints.

Modern techniques of investigation and therapy are described but the importance of the woman herself is never lost sight of and is addressed in the opening chapters.

The 25 authors are all American and the book clearly describes current American practice. Some aspects of gynaecological practice differ from country to country and from one culture to another. Knowing the variety of options can only add to the capabilities of the practising clinician.

Ian D. Duncan

Infection in the Newborn. Perinatal Practice Volume 6 edited by J. de Louvois & D. Harvey. John Wiley & Sons, Chichester 1990, 164 pages, with figures and tables, £39.50

Infectious disease has undergone an almost explosive development as a science in the last decade and this book describes selected topics in the perinatal field where recent advances have been made. The contributors first held a small workshop on neonatal infection but this volume is by no means merely the proceedings of a meeting. Each chapter is a well-referenced and up to date review by an authority in the field.

Neonatologists will find the chapters on rapid diagnostic tests for neonatal bacterial infection, immunoglobulin therapy in neonatal sepsis and antibiotic therapy in the newborn very helpful. Obstetricians will be attracted to the chapters on infection in the mother, and perinatal listeriosis.

Particularly useful is the review of vertical transmission of human immunodeficiency virus, with much valuable data from Italy. This is one of the best discussions I have read on antenatal screening, mode of delivery and breastfeeding in connection with HIV. Immunization of infants of HIV-positive mothers is described and the diagnostic criteria for paediatric HIV infection, a difficult subject, is well set out and referenced.

All obstetricians and neonatologists would enjoy the chapter on the inflammatory response to infection. The author, Michael Levin, describes the basic processes involved in sepsis, ie increased vascular permeability, vasoconstriction/vasodilatation, and microvascular obstruction. The fixed negative charge on the surface of vascular endothelium, tumour necrosis factor, neutrophil elastase and the arachidonic acid pathway controlling platelet activation are very clearly presented with key references and the chapter finishes with therapeutic possibilities, most of them of completely unknown value at least in the clinical field.

I would have liked the editors to have included a complete chapter on the role of microbes in the initiation of preterm labour, as such very important data has emerged in the last five years. Perhaps the series editors are planning a complete book on this subject. This book is really worthy of the title perinatal and is highly recommended.

Andrew Whitelaw

Books received some of which may be reviewed at a later date

Clinical Physiology in Obstetrics Second edition by Frank Hytten & Geoffrey Chamberlain. Blackwell Scientific Publications, Oxford, 1990, 445 pages with figures and tables, £59.50

Practical Statistics for Medical Research by Douglas Altman. Chapman and Hall, London, 1990, 611 pages illustrated with figures and tables, £35.00

Ovarian Endocrinology edited by Stephen Hillier. Blackwell Scientific Publications, Oxford 1991, 195 pages with figures and tables, £69.50

Blackstone's Guide to the Human Fertilisation and Embryology Act 1990. Abortion and Embryo Research. The New Law, by Derek Morgan and Robert G. Lee. Blackstone Press Ltd, 1991, 261 pages paperback, £14.95

Textbook of Fetal and Perinatal Pathology Volumes 1 & 2 edited by Jonathan Wigglesworth and Don B. Singer. Blackwell Scientific Publications, Oxford, 1990. Volume 1, 640 pages. Volume 2, 643–1038 pages, fully illustrated, £195

Detection and Treatment of Early Breast Cancer by Ian S. Fentiman, Martin Dunitz, London/ J. B. Lippincott Co. Philadelphia, 1990, 272 pages fully illustrated, £44.00, US $69.50

Psychological Process of Childbearing by Joan Raphael-Neff. Chapman & Hall, London, 1990, 556 pages £19.95

Infertility Surgery: A Multimethod Approach to Female Reproductive Surgery by John J. Stangel. Prentice Hall International Inc, Connecticut, London, Sydney, 1990, 384 pages £51.50

Methodological Errors in Medical Research edited by Bjorn Anderson. Blackwell Scientific Publications, Oxford, 1990, 278 pages £39.50

Proceedings and Symposiums

Placenta as a Model and a Source edited by Olga Genbacev, Arnold Klopper and Rebecca Beaconsfield. Based on a workshop on Placenta as Model and a Source, held at INEP, Zemun, Yugoslavia, 1988 Plenum Press, New York, London, 1989, US and Canada $49.50, Other countries $59.50

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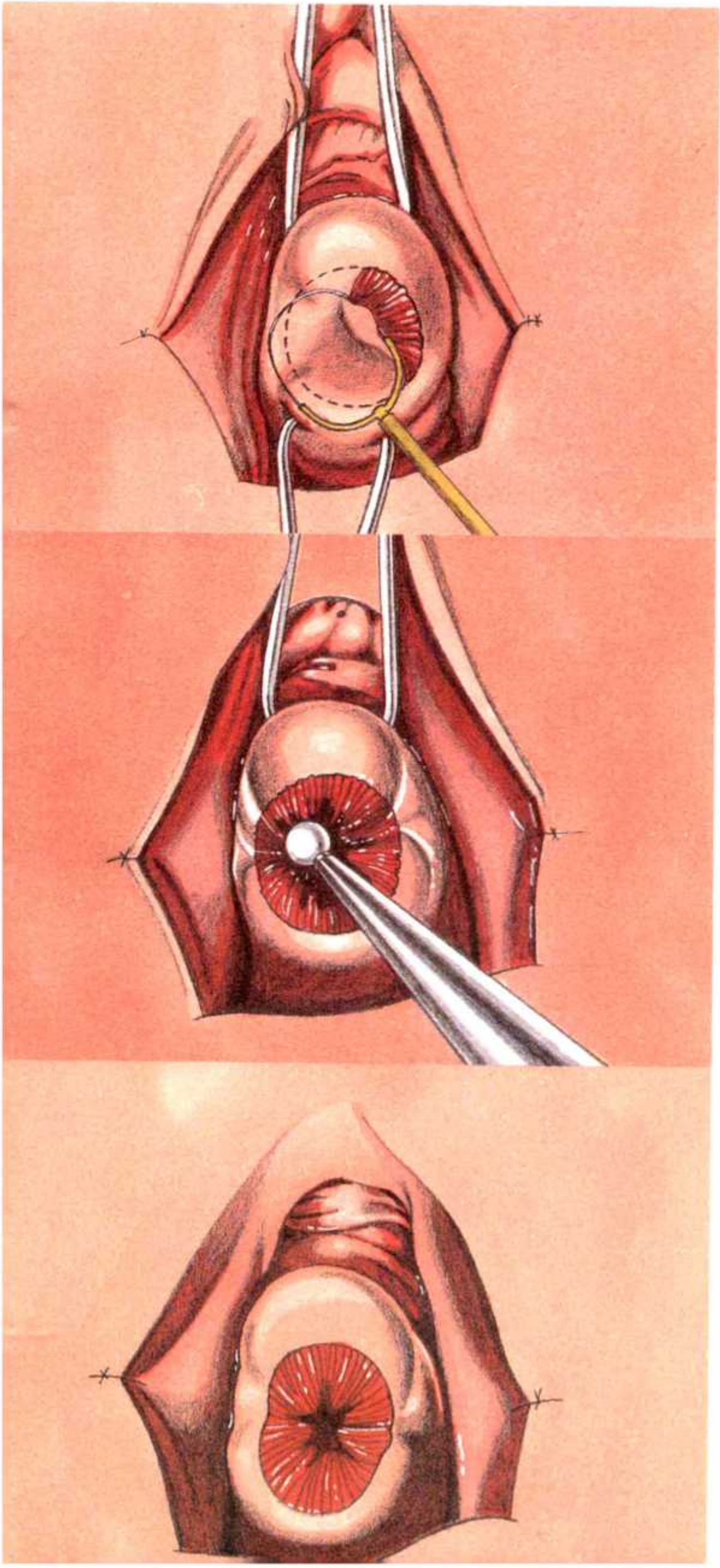

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Edited by David B. Paintin

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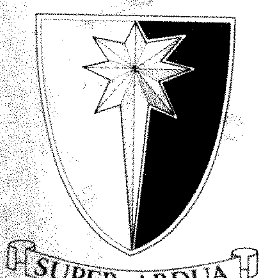

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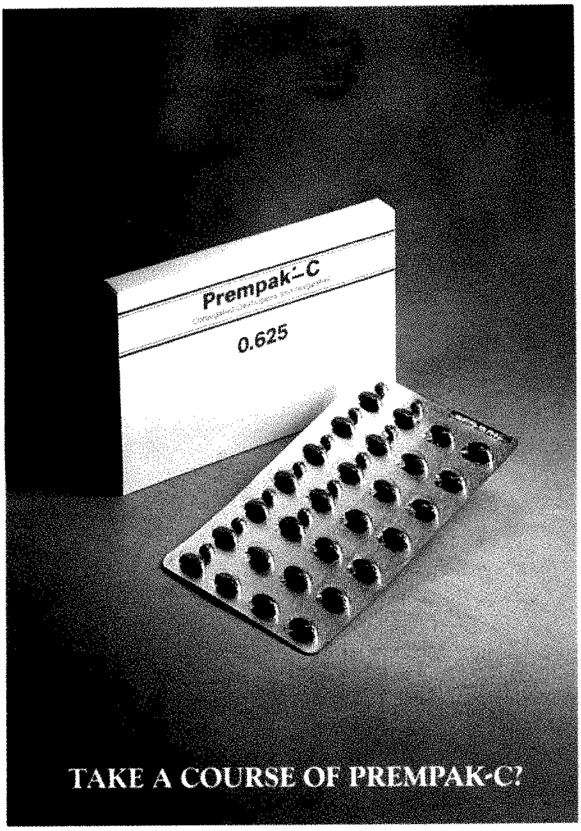

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COMMENTARY

Litigation in obstetrics and gynaecology

The recent failure of a private members bill to introduce a form of no-fault compensation has ensured the continuing high profile of the debate about litigation, particularly as it relates to obstetrics and gynaecology. Both sides view the present system as unsatisfactory The College has claimed (Simmons 1990) that litigation hinders recruitment to the specialty and encourages the practice of defensive medicine. Plaintiffs' organisations complain about the profession's attitude to the injured plaintiff, difficulty in obtaining early and complete discovery of hospital records and the scarcity of experts willing to give evidence on behalf of plaintiffs. Both sides claim to suffer from the slowness of the system and blame the other for exacerbating the inertia; to an outside observer, it might appear that the injured plaintiff had more to lose by delay (Ham *et al.* 1988).

Recent changes have brought improvements for both sides (Kennedy & Grubb 1989; Powers & Harris 1990). The recent extension of legal aid to the infant plaintiff (on the basis of his/her own resources, rather than those of the parents) has righted an obvious wrong but has not been welcomed by some on the defendants' side. Recent procedural improvements have addressed the 'blind man's buff' (Donaldson 1986) inherent in the tort procedure. For the past 3 years it has been standard for the summons for directions to require the exchange of expert evidence in the form of written reports, including opinions on liability, before trial; previously neither side knew what the opposing experts might say in oral evidence. Sometimes there is an exchange of witness statements before the final expert report so that each side's experts can actually have a common basis of facts on which to give an opinion. There have even been recent examples (Keane v Plymouth Health Authority 1988 unreported, Bayer v Clarkson 1989) of trials conducted in a more logical sequence. The practice has always been for the plaintiff's case to be given first so that the plaintiff's experts have no knowledge of what the defendants' factual witnesses will say By re-arranging the trial so that the facts on both sides are produced first, both experts have the opportunity in the second phase of the trial to comment on the full facts. Not only is this inherently fair to both sides but a great deal of time is saved. Until such a system becomes the norm, the proceedings will remain unsatisfactory. The Rules of the Supreme Court now permit a 'without prejudice' meeting of experts before trial so as to discuss their respective opinions, agree on common ground and narrow the areas of difference. Surprisingly, this rarely happens, although the rules give the Court the power to order such a meeting.

Further reforms are advocated. Defendant lawyers want changes in law and procedure, particularly a drastic cut in the period of limitation (Capstick *et al.* 1991); plaintiff organisations want further procedural reform and a greater willingness on the part of the profession to continue caring for the injured plaintiff. Who wants no-fault? Certainly not the victim of a negligent accident (Leigh 1990) for no scheme yet proposed would begin to compensate victims at the same level as does the present adversarial tort system; certainly the victims of non-negligent accidents would welcome it but then what is an accident? Is rubella infection an accident, or placental insufficiency? Proponents of no-fault compensation conveniently forget that liability has two legs; the plaintiff has not only to prove negligence but also causation; do away with the need to prove negligence and you are still left with the causation argument which will be unchanged by no-fault compensation. The professional literature has been flooded recently with 'evidence' that cerebral palsy is infrequently related to birth accidents (even an orchestration of the literature is alleged) because everyone involved in the process knows that causation is the difficult part of the argument; the negligence is usually fairly clear, one way or the other.

But why stop at medical accidents? Should the victim of a road accident have to prove negligence and causation before obtaining damages, while the birth-palsied child need only prove that there was an 'accident'? And is the victim of the road traffic accident to be better compensated through the tort system than can be the victim of the medical accident through a cash-limited no-fault scheme? Here are two kinds of justice for the same kind of brain damage (Puxon 1991). The truth is that only the victims of non-negligent accidents (and those adults who could not affford to litigate) would benefit from such a two tier system. No other accident victims would be helped; the victims of the medical accident still have to resort to the tort system to get a level of compensation comparable with the road traffic accident. But what of the profession? The idea of medical compensation coming out of a separate treasury pot so as not to diminish the resources of health authorities is clearly attractive; but the profession should beware of any system of compensation which reduces professional accountability. Mrs Currie probably had it right 'I do not feel that we should be aiming to introduce no-fault compensation. We should be aiming at fewer faults' (Hansard 1991).

The present system is seen as promoting defensive medicine but what is defensive medicine? In the pejorative sense it imports clinical interference that is for the benefit of the doctor and not of the patient. In another sense it involves the observation of adverse outcome and the change of clinical practice to reduce the incidence. Some would call that medical audit. I suspect that one man's defensive medicine is another man's risk management.

The practice of proper risk management has been prevented in the past by the diversity of agencies responsible for the defence and compensation of malpractice. The advent of NHS indemnity provides an opportunity for health authorities to put their house in order. The process involves two distinct stages. The first or clinical stage of risk management is the identification of adverse outcome, as an extension of medical audit. This allows the defendant to identify the potential litigation at the same time as the plaintiff. In the past the first intimation of a legal action has come after an interval of several years with the 'letter before action'. To a large extent this aspect of risk management overcomes the problem of the limitation period, the plaintiff being able to sue some years after the event happened. The second phase of risk management involves aggressive case management, once the action begins. There has been no tendency in the past for health authorities to instruct solicitors in the full sense of controlling the course of the action, but they have simply handed over the case to a firm of solicitors without client intervention or instruction. Similarly the individual doctor has never been in a position to give personal instructions to his own defending solicitor, but has needed to rely on the Medical Defence Organization (MDO); in general the solicitors have called the tune. The result of this 'Management by inertia' has been years of wasted costs with cases settled at the door of the court or—as in one recent case—halfway through the plaintiff's evidence, cases which should have been settled years earlier and at a fraction of the cost. With the new arrangements for indemnity at unit level there should be less incentive to postpone the inevitable settlement into another financial year.

It is against this background that the publication of the College booklet 'How to Avoid Medico-Legal problems in Obstetrics and Gynaecology' (Chamberlain & Orr 1990) must be read. The booklet is the work of the medicolegal committee and its publication is most welcome. The book contains three sections. The first on basic concepts contains two excellent chapters by Charles Butcher explaining the civil wrong of tort and the process of a claim, Dr A. W. Miller describes the work of the expert witness in the preparation of reports; there is a further chapter (now overtaken by NHS indemnity) on the role of the medical defence organizations.

The remaining two sections are clinical dealing respectively with obstetrics and gynaecology. The clinical sections set the benchmark for competent practice in sensitive areas and due prominence is given to birth related injuries (Professor Symonds) and to sterilization (Dr C. Orr). These two areas account for the majority of litigation.

Professor Symonds' remarks in relation to intrapartum assessment are particularly helpful, drawing attention to the necessity of a proper tocograph recording in order to assess the significance of the cardiograph. He also emphasises the need for 'some action' to be taken in the presence of an abnormal trace. It is no use pretending that cardiotocographs (CTGs) have no predictive value in labour (Murphy *et al.* 1990). Why else would we continue to use them in most of our labour wards? The debate on the interpretation of CTGs was not helped by the recent lecture by the Chief Medical Officer (CMO) of the Department of Health (Acheson, 1990; 1991), some of whose points were subsequently challenged in the press (Sharif 1991). Whilst the CMO is right to observe that only a minority of cases of cerebral palsy are associated with birth asphyxia—the current estimates are around 10% (Hall 1989; Grant *et al.* 1989)—he was on less safe ground when he continued 'even in the minority where asphyxia does occur this is not necessarily avoidable'. An independent review of cerebral palsy litigation reported to the MPS in the period 1982–1986 concluded that either the obstetrician or the system of care had been at fault in 86% of cases (Ennis & Vincent 1990).

Other chapters on congenital abnormalities and genetic testing and on AIDS perhaps give warning of areas that, in the future, may be ripe for litigation. Whilst the advice given in the clinical sections is clearly of great help to the profession, I suspect that in future years it may prove an invaluable aid to the plaintiff in setting a standard, approved by the College, for reasonable competence.

The implication throughout the book is that plaintiffs only seek money as redress for their injuries but this is not the experience of plaintiffs' experts. Motivation is much more complex; often patients want only an explanation and an apology which, if provided at an early stage, could prevent much litigation. The real answer to the question 'How to avoid medico-legal problems in obstetrics and gynaecology?' is good practice and good communication. Whilst the former will provide a perfect defence to litigation, the latter (irrespective of the standard of care) will often obviate it.

Chapter one is an unfortunate opening for the book: it contains a number of statements which are in conflict with later chapters. A single editor with a firm hand might have prevented some of the confusion and contradiction. Passing reference to the 'Inbuilt advantage to doctors' needs expansion and the burden of proof explained. The courts do not require issues to be judged in black and white but only on the balance of probabilities. Reference to clinicians who 'judge their colleagues' is unfortunate. The proper role of the expert is defined by Dr Miller in an excellent chapter five, which could profitably be expanded. British law on consent was clearly enunciated by the House of Lords in Sidaway (1985) and references to the American system only cause anxiety and confusion. Not all defensive medicine is bad for the patient, viz., continuous cardiac monitoring under general anaesthesia. It comes as a surprise to learn that 'No medical defence organization would settle a case without the knowledge or consent of the doctor concerned.' Unfortunately they have been known to do so. Resource limitations and lack of equipment were clearly addressed by the Court of Appeal in Wilsher (1986); the implications of that judgement are explored in chapter two. An uninformed comment in chapter 1 on the legal aid system is redressed in chapter four and the last sentence of the chapter is simply wrong. In all litigation involving a legally aided plaintiff (except in the Court of Appeal) the successful defendant is unable to recover costs; it is not a misfortune peculiar to medical negligence litigation. Chapter one urgently needs rewriting.

The section on Crown Indemnity in the opening chapter is all gloom and the gloom is not lifted by chapter three which is a thinly disguised attempt by the secretaries of the medical defence organizations to justify their continued role in the new system. Crown Indemnity does have some advantages to both plaintiff and defendant; whilst it is unrealistic to expect the MDOs to recognize these advantages, College members should be aware that the change is far from being all loss particularly if the health authorities take the opportunity to develop expertise in risk management.

The two main omissions from the book might perhaps be addressed in later editions. The first is any mention of risk management. The culture change required to bring this about is now being addressed by a number of agencies and has found echoes in the medical press (Dingwall 1991). The College should give a lead for it is in this area where, without any prejudice to the injured plaintiff, the profession could prevent money passing needlessly into the pockets of lawyers. The second major defect is the lack of any concern for the injured plaintiff. What is needed is firm guidance by the College on how the clinician should react after a medical accident, circumstances in which the caring often seems to stop.

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Vaginal infection and preterm labour

H. M. McDONALD, J. A. O'LOUGHLIN, P. JOLLEY, R. VIGNESWARAN, P. J. McDONALD

Abstract

Objective—To study the vaginal flora of women in preterm labour (PTL) and determine whether the presence of specific vaginal microflora is significantly associated with onset of PTL.

Design—A comprehensive prospective study of the vaginal microflora of women in early labour comparing women in PTL with term controls. Microbiological assessment included cultures for aerobic and anaerobic bacteria, yeasts, genital mycoplasmas and *Trichomonas vaginalis*. Multiple logistic regression analysis was used to adjust for confounding obstetric and demographic variables.

Setting—The Queen Victoria Hospital, Adelaide.

Patients—428 Women in PTL compared to 568 women in labour at term.

Main outcome measure—PTL and preterm prelabour rupture of membranes (PPROM) in relation to specific vaginal microflora.

Results—After multiple logistic regression analysis, two distinct bacteriological groupings were associated with PTL <37 weeks gestation, namely, the bacterial vaginosis group of organisms, *Gardnerella vaginalis* and *Bacteroides* spp., and a group of enteropharyngeal organisms, *E. coli*, *Klebsiella* spp., *Haemophilus* spp. and *S. aureus*. *G. vaginalis* was found in 12% of women in PTL compared to 6% at term [regression odds ratio (ROR) 1·8, 95% confidence intervals (CI) 1·1–3·1] whereas *Bacteroides* spp. were detected in 45% of women in PTL compared with 35% at term (ROR 1·6, CI 1·2–2·1). The prevalence of *G. vaginalis* (17%) and *Bacteroides* spp. (50%) was even higher in women in PTL <34 weeks gestation. The enteropharyngeal group of organisms were more commonly present in women in PTL <37 weeks (*E. coli* 10% *vs* 6%, ROR 1·4, CI 0·8–2·4; *Klebsiella* spp. 3% *vs* <1%, ROR 5·4, CI 1·1–26·7; *Haemophilus* spp. 2% *vs* <1%, ROR 5·5, CI 1·1–28·6; *S. aureus* 6% *vs* 4%, ROR 1·8, CI 0·9–3·3) and were isolated even more frequently in women in PTL <34 weeks (*E. coli* 15%; *Klebsiella* spp. 4%; *S. aureus* 7%). *Bacteroides* spp., *Klebsiella* spp., and *Haemophilus* spp. were all found to be associated with PPROM.

Conclusion—There are two distinct bacteriological groupings commonly found in women in PTL, especially in PTL <34 weeks gestation. These bacteriological groups are women with bacterial vaginosis in pregnancy and women who demonstrate enteropharyngeal bacteria in the vagina.

Despite major advances in obstetric and neonatal care over the past two decades, the preterm birth rate has remained nearly constant at 7–10% of pregnancies. In approximately 50% of preterm births no cause is found for preterm labour or prelabour rupture of the membranes

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(PROM). However, a growing body of evidence suggests that maternal genital tract infection is associated with preterm labour. Such evidence is based on studies showing recovery of organisms from the amniotic fluid of women in preterm labour (Romero *et al.* 1989b), histological evidence of chorioamnionitis (Guzick & Winn 1985), and a reduction in the birth of immature babies with antibiotic treatment of pregnant women with threatened preterm labour (McGregor *et al.* 1986). Certain specific maternal vaginal organisms have been linked to preterm labour and PROM. The vaginal or cervical carriage of *Neisseria gonorrhoeae* (Amstey *et al.* 1976), group B streptococci (Regan *et al.* 1981; Alger *et al.* 1988; McDonald *et al.* 1989), *Chlamydia trachomatis* (Gravett *et al.* 1986b; Martius *et al.* 1988; Alger *et al.* 1988), *Mycoplasma hominis* (Munoz *et al.* 1989) *Trichomonas vaginalis* (Minkoff *et al.* 1984), and bacterial vaginosis (Gravett *et al.* 1986a, b) have all been associated with increased rates of preterm birth. However, other studies have failed to confirm some of these associations (Martius *et al.* 1988; Romero & Mazor 1988) Reported studies in general have focused on a single organism without simultaneously investigating other organisms present, or interactions between them. In addition, many of these studies have not taken account of other confounding clinical, demographic and social variables that may predispose to preterm labour.

For this reason, a comprehensive prospective study of nearly 1000 women was undertaken, to investigate all possible associations between vaginal carriage of different organisms and preterm labour. Demographic and other variables were recorded and considered in assessing the results.

Subject and methods

In a prospective study at the Queen Victoria Hospital between October 1986 and October 1989, the vaginal flora of 428 women in preterm labour (<37 weeks gestation) was compared with that in 568 women in labour at term (⩾37 weeks gestation). Vaginal swabs were taken from all women on admission to hospital in preterm or threatened preterm labour. Those in threatened preterm labour who were not delivered within 7 days and before 37 weeks gestation were excluded from this analysis. Women with complications which required induction of labour or elective caesarian section were also excluded from the study. As the Queen Victoria Hospital is a tertiary referral obstetrics hospital, 25% of women in the preterm labour group were transferred from other hospitals, just before or during preterm labour. The comparison group of 568 women sampled in term labour were enrolled consecutively on admission to the labour ward. The criterion for enrolment was the booking allocation to one of the four obstetric units of the hospital, under the control of one of the authors. (The unit allocation process occurs at the booking visit and is randomized.)

Three swabs were taken from the posterior vaginal fornix using a speculum with a non-bacteriostatic lubricant. The swabs were placed in Stuart's, Amies and anaerobic (B-D Vacutainer) transport media for culture of all aerobes, mycoplasmas and anaerobes. Direct smears on glass slides were made and the swabs cultured on horse blood agar (BP), chocolate agar (CHOC), human blood agar (HB), cystine lysine electrolyte deficient agar (CLED), Sabouraud's agar (SAB), gonococcal agar (GC), Sheppard's A7 Ureaplasma differential agar (UD), brain heart infusion agar (BHI), BHI plus kanamycin and vancomycin (BKV), trichomonad broth (TRI) and two cooked meat broths (CMM). The BP, CHOC, HB, GC and UD plates were incubated in 5% CO_2, the CLED and SAB plates in air; and the BHI and BKV plates in an anaerobic atmosphere for 4 days. One cooked meat broth was subcultured to BP and incubated aerobically for 18–24 h. The other cooked meat was subcultured to BHI and to BKV which were incubated anaerobically for 2–4 days.

Growth on the plates was semiquantified as described by Rotheram & Schick (1969). All isolates were identified according to standard laboratory procedures. *Gardnerella vaginalis* was identified by β-haemolysis on the HB plate, together with appropriate appearance under Gram stain, resistance to sulphonamide diagnostic disc (1000 μg) and sensitivity to metronidazole (50 μg). The isolation of *G. vaginalis* was based on a non-selective plate so that women with only scant growth of *G. vaginalis* would not be detected by this method. All streptococci were serotyped using the Phadebact or Streptex methods. Gram negative isolates, both aerobic and anaerobic, were identified using the Vitek Automicrobic System, as were the *Neisseria, Haemophilus* and yeast isolates. *Mycoplasma hominis* and *Ureaplasma urealyticum* isolates were identified by typical morphology on UD agar. Anaerobes which grew in <4 days were separated into penicillin resistant or sensitive. Penicillin resistant strains were further identified by the Vitek Automicrobic System into *B. fragilis* or other *Bacteroides species*. *Fusobacterium species* were identified by the Vitek system. *Peptostreptococcal* species were not further identified.

Chlamydia trachomatis fluorescent tests were discontinued from the study as the prevalence of *C. trachomatis* in our antenatal population is very low (1% in previous pilot study of 100 women). Routine viral culture for herpes simplex was not performed during the study.

The information recorded included all associated obstetric factors known to place a woman at risk of preterm labour, such as multiple pregnancy, previous spontaneous preterm delivery, previous mid-trimester miscarriage, cervical incompetence, polyhydramnios (ultrasound confirmed), pyelonephritis, uterine malformations, or placenta praevia after 22 weeks with bleeding. Also recorded were maternal age, gravidity, parity, gestational age at delivery (determined by combination of last menstrual period and first or second trimester ultrasonography), PROM before 37th week of gestation, tocolytic therapy, birthweight, neonatal clinical assessment, laboratory investigations, placental histopathology and microbiology. PPROM was defined as rupture of the membranes at least 1 h before any other signs of labour, and confirmed by the presence of alkaline fluid in the vagina and the presence of ferning, in women who were delivered before 36 completed weeks.

Statistical analysis

Univariate comparisons of proportions were performed using the χ^2-test with Yates' correction for small numbers. Odds ratios and 95% confidence intervals were calculated. Multivariate logistic regression analysis was peformed using the GLIM statistical software programme, to take into account obstetric risk factors predisposing to preterm labour and confounding demographic variables. A fitted model using stepwise backwards elimination was used in the regression analysis.

This study was approved by the QVH ethics committee, and participating patients gave informed consent.

Results

During the study period 57% of women in preterm labour who were eligible for inclusion in the study had swabs taken in early labour, (although 6% of these were later excluded as they did not include anaerobic culture). The remaining 43 per cent did not have swabs taken, usually due to the rapidity of the labour. Hence the actual number of women in preterm labour who were successfully enrolled in the study was 428.

Demographic characteristics of the women in the preterm and term groups are shown in Table 1. There was no significant difference in the percentage of women <17 years or >35 years of age between the preterm and term groups, although the mean age differed significantly between the two groups. Because reliable smoking information was not available for many women in the preterm group it was not possible to include smoking in this analysis, although a limited comparison revealed a significantly higher number of smokers in the preterm group than the term group (47% *vs* 39%) (Table 1). Age and parity were taken into account in the multivariate analysis, however, stepwise backwards analysis resulted in eventual elimination of these factors from the fitted model. As would be anticipated, those women with preterm labour had significantly more predisposing factors than those who laboured at term (Table 2). In construction of the regression model, women with placenta praevia after 22 weeks with bleeding, cervical incompetence, polyhydramnios, uterine malformation and pyelonephritis had to be excluded, because of the very low numbers in the term group (Table 2). Previous preterm delivery, previous midtrimester miscarriage and multiple pregnancy were factors found to be significantly associated with preterm labour and were fitted into the regression model.

Results of univariate analysis showed significant associations between the presence of *G. vaginalis* and *Bacteroides* spp. and preterm labour <37 weeks. *G. vaginalis* was found in 12% of preterm women compared with 6% of term women ($P<0{\cdot}01$), while *Bacteroides* spp. were also found in significantly higher numbers of preterm women (Table 3). The associations between *G. vaginalis* and *Bacteroides* spp. and preterm labour remained significant when multiple logistic regression analysis was performed to take account of demographic and obstetric risk factors. Other organisms associated with bacterial vaginosis such as *M. hominis* and *U. urealyticum* did not show a significant

Table 1. Demographic characteristics of the women in the study

Variable	Preterm (<37 weeks) n=428	Term (≥37 weeks) n=568	Significance Test	Significance *P* value
Maternal age (years)	27·0 (5·4)	26·1 (5·2)	t=2·52	<0·05
Gestation (weeks)	32·5 (3·5)	39·9 (1·1)		
Mean birth weight (g)*	2099 (707)	3388 (449)		
Nulliparous	206 (48%)	299 (53%)	χ^2=1·8	>0·05
Smokers	155/328 (47%)	202/525 (39%)	χ^2=6·4	<0·05

* excluding multiple pregnancies.
Results are mean (SD) values or number (%) as appropriate.

association with preterm labour when tested independently or by multivariate analysis. Analysis of individual *Bacteroides* species showed all were associated with preterm labour, hence they were considered as a group *Bacteroides* spp. in the analysis.

Significant associations were also shown between preterm labour and a second group of entero-pharyngeal organisms, *E. coli, Klebsiella* spp., and *Haemophilus* spp. (Table 3). *E. coli* was detected in the vaginal swabs of 10% of women in preterm labour. This was nearly twice the carriage rate of those who progressed to term labour. Other coliforms were also implicated e.g. *Klebsiella* species (*K. pneumoniae* or *K. oxytoca*) were found in 3% of women in preterm labour compared to <1% at term. *Haemophilus* species (*H. influenzae* or *H. parainfluenzae*) occurred in a higher proportion of preterm women compared with the term group. This association became significant after multiple logistic regression analysis. *S. aureus* was more common in women in preterm labour although this finding was not statistically significant (Table 3).

No significant associations were demonstrated between carriage of other aerobes, anaerobes or genital mycoplasmas and preterm labour. No differences were detected in the prevalence of *M. hominis, U urealyticum,* group B streptococci, or *C. albicans.*

Preterm PROM was found to be significantly associated with the presence of *Bacteroides* spp., *Haemophilus* spp., and *Klebsiella* spp. (Table 4). These associations remained strongly significant after multiple logistic regression analysis. *G. vaginalis* was not found to be associated with preterm PROM, however, in women with intact membranes and preterm labour <37 weeks, the presence of *G. vaginalis* was strongly associated with preterm labour when compared with the term group (15% *vs* 6% regression odds ratio 2·2, 95% CI 1·2–4·2,*P*<0·05). No other organisms were significantly associated with preterm labour <37 weeks with intact membranes.

Given that the most serious neonatal effects of immaturity usually occur in infants born before 34 weeks gestation, the prevalence of these vaginal pathogens in women in preterm labour < 34 weeks gestation was examined and com-

Table 2. Obstetric risk factors predisposing to preterm labour

	Preterm (n=428) n (%)	Term (n=568) n (%)	Odds ratio	95% CI	*P* value
Previous preterm delivery (>20 weeks)	71 (17)	23 (4)	4·27	2·78– 6·57	*P*<0·001
Previous midtrimester miscarriage	21 (5)	11 (2)	2·60	1·28– 5·29	*P*<0·05
Multiple pregnancy	52 (12)	4 (1)	8·63	5·00–14·87	*P*<0·001
Cervical incompetence	14 (3)	1 (0)	8·04	2·87–22·51	*P*<0·001
Polyhydramnios (ultrasound confirmed)	13 (3)	1 (0)	7·87	2·71–22·82	*P*<0·001
Uterine malformation	1 (0)	2 (0)	0·67	0·07– 6·65	ns
Pyelonephritis during pregnancy	1 (0)	2 (0)	0·67	0·07– 6·65	ns
Placenta praevia after 22 weeks with bleeding	10 (2)	0 (0)	9·53	2·73–33·36	*P*<0·001
With one or more risk factors	148 (35)	40 (7)	6·03	4·38– 8·31	*P*<0·001

Table 3. Vaginal flora isolated from the women in the study

Organism	Preterm (*n*=428) [*n*=391] *n* (%)	Term (*n*=568) [*n*=562] *n* (%)	Odds ratio	95% CI	*P* value
G. vaginalis	50 (12)	35 (6)	2·0	1·3– 3·2	*P*<0·01
			[1·8]	[1·1– 3·1]	[*P*<0·05]
Bacteroides spp	194 (45)	201 (35)	1·5	1·2– 1·9	*P*<0·05
			[1·6]	[1·2– 2·1]	[*P*<0·01]
E. coli	41 (10)	33 (6)	1·7	1·1– 2·8	*P*<0·05
			[1·4]	[0·8– 2·4]	[ns]
Klebsiella spp.	12 (3)	2 (<1)	8·2	1·8–36·4	*P*<0·01
			[5·4]	[1·1–26·7]	[*P*<0·05]
Haemophilus spp.	7 (2)	3 (1)	3·1	0·8–12·1	ns
			[5·5]	[1·1–28·6]	[*P*<0·05]
S. aureus	26 (6)	22 (4)	1·6	0·9– 2·9	ns
			[1·8]	[0·9– 3·3]	[ns]
Group B streptococcus	34 (8)	52 (9)	0·9	0·6– 1·4	ns
Peptostreptococcus spp.	47 (11)	80 (14)	0·8	0·5–1·1	ns
M. hominis	21 (5)	26 (5)	1·1	0·6– 1·9	ns
U. urealyticum	144 (34)	189 (33)	1·0	0·8– 1·3	ns
C. albicans	65 (15)	99 (17)	0·9	0·6– 1·2	ns

ns=not significant. Figures in square brackets denote values after multiple logistic regression analysis.

pared with women with PTL delivered between 34 and 36 weeks gestation. The demonstrated association between the bacterial vaginosis organism *G. vaginalis* and preterm labour, became much stronger when 34 weeks gestation was used as a reference point [the prevalence of *G. vaginalis* in the <34 week group (17%) was more than twice the prevalence in the 34–36 week group (7%) and remained significant after adjustment by multiple logistic regression] (Table 5). The prevalence of two of the entero-pharyngeal organisms, *E. coli* and *Klebsiella* spp, was nearly four times higher in preterm women <34 weeks gestation than in women delivered between 34–36 weeks and a strong association was demonstrated between the pres-

Table 4. Vaginal flora isolated from women with preterm prelabour rupture of membranes (PPROM) compared with women delivered at term

Organism	PPROM (*n*=248) [*n*=229] *n* (%)	Term (*n*=568) [*n*=562] *n* (%)	Odds ratio	95% CI	*P* value
G. vaginalis	23 (9)	35 (6)	1·6	0·9– 2·7	ns
			[1·4]	[0·7– 2·7]	[ns]
Bacteroides spp.	116 (47)	201 (35)	1·6	1·2– 2·1	*P*<0·01
			[1·7]	[1·2– 2·4]	[*P*<0·01]
E. coli	22 (9)	33 (6)	1·6	0·9– 2·8	ns
			[1·4]	[0·7– 2·6]	[ns]
Klebsiella spp.	8 (3)	2 (<1)	9·4	1·9–47·4	*P*<0·01
			[6·9]	[1·3–36·3]	[*P*<0·05]
Haemophilus spp.	6 (2)	3 (1)	4·7	1·2–18·8	*P*<0·05
			[8·7]	[1·6–46·0]	[*P*<0·01]
S aureus	14 (6)	22 (4)	1·5	0·8– 3·0	ns
			[1·6]	[0·8– 3·4]	[ns]

ns=not significant. Figures in square brackets denote values after multiple logistic regression analysis

Table 5. Vaginal flora isolated from women with preterm labour at <34 weeks gestation *vs* 34–36 weeks gestation

Organism	Preterm <34 weeks ($n=214$) [$n=188$] n (%)	Preterm 34–36 weeks ($n=214$) [$n=203$] n (%)	Odds ratio	95% CI	P value
G. vaginalis	36 (17)	14 (7)	2·9	1·5– 5·5	$P<0·001$
			[3·2]	[1·5– 6·7]	[$P<0·01$]
Bacteroides spp	106 (50)	87 (41)	1·4	1·0– 2·1	ns
			[1·2]	[0·8– 1·9]	[ns]
E. coli	32 (15)	9 (4)	4·0	1·9– 8·6	$P<0·001$
			[5·2]	[2·2–12·1]	[$P<0·001$]
Klebsiella spp.	9 (4)	3 (1)	3·1	0·8–11·6	ns
			[2·1]	[0·5– 9·0]	[ns]
Haemophilus spp.	3 (1)	4 (2)	0·8	0·2– 3·4	ns
			[0·8]	[0·2– 4·3]	[ns]
S. aureus	16 (7)	10 (5)	1·7	0·7– 3·7	ns
			[1·6]	[0·7– 3·9]	[ns]

ns=not significant. Figures in square brackets denote values after multiple logistic regression analysis.

ence of *E. coli* and preterm labour <34 weeks (Table 5). *S. aureus* was also more common in women in preterm labour <34 weeks (Table 5).

Clinical signs of infection, i.e., a raised white cell count (>15 000) raised CRP(>12μg/ml) or suspected chorioamnionitis were noted in 35% of women in preterm labour compared with 2% of term women. These clinical signs of infection were more common in the enteropharyngeal preterm labour group than in the *G. vaginalis* preterm labour group (49% *vs* 38%), although this difference was not statistically significant. Histopathological examination of the placenta, membranes and cord from 198 women was made because of clinical signs of infection or preterm labour. Of these, 184 placentas were from women delivered at <37 weeks gestation and 14 from symptomatic women ≥37 weeks gestation. Twenty-five placentas from women delivered at term were examined for use as controls. Chorioamnionitis confirmed by histopathology occurred in 65 of 184 (35%) women with preterm labour and in none of the 25 term controls. The prevalence of chorioamnionitis was higher in the enteropharyngeal than in the *G. vaginalis* preterm group (44% *vs* 31%), although this was not statistically significant. *U. urealyticum* was the most frequent isolate from preterm placentas, occurring in 24% of preterm placentas cultured. Amniotic fluid obtained by amniocentesis was cultured from 27 women in preterm labour, 20 of whom had clinical signs of infection. *Ureaplasma urealyticum* was the most frequently isolated organism, occurring in 4 of 27 amniotic fluids. The remaining amniotic fluid isolates were *S. sanguis* (2), *S. aureus* (1), group B streptococcus (1) *C. albicans* (1), *Bacteroides* spp. (1), *Peptostreptococcus* (1), and *S. epidermidis* (1).

Discussion

Two substantive observations have emerged from this study. Firstly, we have confirmed significant associations between the bacterial vaginosis group of bacteria, (*G. vaginalis*, and *Bacteroides* spp.) and preterm labour. These associations remained significant when obstetric risk factors predisposing to preterm labour and confounding variables such as age and parity were taken into account using multiple logistic regression analysis.

Eschenbach *et al.* (1984) reported the first case-control study suggesting an association between bacterial vaginosis and low birth weight. These workers compared the prevalence of bacterial vaginosis, as defined by abnormal gas liquid chromatography (GLC) patterns, from vaginal secretions in 57 women who gave birth preterm, with a control group of 114 women at term. However, Minkoff *et al.* (1984) reported a prospective study of 233 patients sampled at the time of their first antenatal visit and failed to demonstrate a significant association between bacterial vaginosis and preterm labour. Bacterial vaginosis was defined clinically in that study and, in our experience, such definition lacks objectivity and is not a reliable indicator of the vaginal bacterial status. Further confirmation of the significance of bacterial vaginosis was supplied by Gravett *et al.* (1986a) who found an association between bacterial vaginosis, defined by abnormal GLC patterns, and preterm labour in a study of 534 women. Bacterial vaginosis was associated with PROM in both of these studies. More recently, Martius *et al.* (1988) reported a case-control study of 97 women in preterm labour and 115 women at term, and found that the preterm group were more likely to have bacterial vaginosis than the term group ($P=0{\cdot}03$). Bacterial vaginosis was defined by Gram staining of vaginal fluid. Our results, derived from a much larger comprehensive study supported by multiple logistic regression analysis, confirm the previous findings of Eschenbach *et al.* (1984), Gravett *et al* (1986a) and Martius *et al.* (1988), and in our view, categorically establish an association between bacterial vaginosis and preterm labour.

An important observation from our study concerned the highly significant association demonstrated between *G. vaginalis*, and preterm labour <34 weeks gestation. This contrast with Gravett *et al.* (1986b) who reported a significant association between bacterial vaginosis and preterm labour <37 weeks gestation but not at <34 weeks gestation. We also observed that *Bacteroides* spp was significantly associated with preterm PROM, whereas *G. vaginalis* was not. This supports the findings of Minkoff *et al.* (1984), who showed that women with *Bacteroides* spp. had a relative risk of 2·8 for PROM compared with non-carriers.

The second and major finding of our study was the significant associations between *E. coli, Klebsiella* spp., *Haemophilus* spp., and *S. aureus* (borderline significance), preterm labour and PPROM. Unlike the bacterial vaginosis group, these are all virulent organisms which often cause sepsis soon after acquisition. As a group, these organisms normally colonize either the nasopharyngeal region (*S. aureus*) or the lower bowel (*E. coli, Klebsiella* spp.). Pharyngeal carriage of *H. influenzae* occurs in 5–10% of the population, and in the majority of chronic bronchitics. Individual case reports of amnionitis and preterm labour due to these organisms have been described (Friesen & Cheng 1986, Gibbs *et al.* 1982). However, they have not so far been reported in previous studies on vaginal flora and preterm labour, presumably because they were not targeted. The size, the comprehensive nature of the cultures, and the use of multiple logistic regression in this study ensured that all pathogens were targeted, and statistical analysis of results would take into account confounding obstetric and demographic variables.

Some recent studies have reported an association between *M. hominis* and *U. urealyticum* and preterm labour (Gravett & Eschenbach 1986; Lamont *et al.* 1987; Munoz et al 1989). Our study did not confirm such an association Our results are consistent with the conclusions of Romero & Mazor (1988) who, in a review of studies on infection and preterm labour, determined that there was insufficient evidence to support such an association. There is, however, justifiable interest in *M. hominis* and *U urealyticum*, as there appears to be an association between histologic chorioamnionitis and the isolation of *U. urealyticum* in placenta (Embree *et al.* 1980). Furthermore it is known that *M. hominis* may be present in large numbers in bacterial vaginosis (Eschenbach 1989).

We have reported previously an association between vaginal group B streptococci carriage and preterm labour, but such an association was not found in the present study, possibly because vaginal swabs were taken from the posterior vaginal fornix area instead of the lower vagina as in our previous study (McDonald *et al.* 1989). As rectal and low vaginal carriage of group B streptococci has been reported at a higher prevalence than carriage in the upper vagina, the site swabbed may have some bearing on these conclusions. Nevertheless several other investigators have failed to confirm an association between group B streptococci and preterm labour (Hastings *et al.* 1986, Minkoff *et al.* 1984) and the situation remains unresolved.

We conclude that there are two distinct bacteriological groupings commonly found in women in preterm labour. The first is characterized by the bacterial vaginosis group of micro-organisms. Women with bacterial vaginosis often do not have symptoms of vaginitis, and there is an absence of inflammation. The mechanisms through which these micro-organisms may contribute to the onset of preterm labour are not clear. It is known that the numbers of *G. vaginalis* present in women with bacterial vaginosis are usually 100 times greater than those without bacterial vaginosis; furthermore the numbers of anaerobic bacteria are commonly 1000 times higher (Spiegel *et al.* 1980). It has been postulated that large numbers of certain bacteria may stimulate labour preterm by the production of high levels of phospholipase. Phospholipase releases the arachidonic acid bound to fetal chorioamnion and maternal decidua tissue. As arachidonic acid is the precursor of prostaglandins, a cascade of prostaglandins may be produced thus initiating preterm labour. The highest levels of phospholipase are produced by *G. vaginalis, B. fragilis* and other anaerobic bacteria (Bejar *et al.* 1981). Whilst this is a biochemically attractive hypothesis, it remains unproven. The physiological state of the vagina colonized with bacterial vaginosis flora is altered from the normal (e.g., pH change), and one could just as easily advance the hypothesis that such alterations may sensitize receptors responsible for initiating labour in response to otherwise 'normal' stimuli. Bacterial vaginosis in non-pregnant women has been associated with multiple sexual partners, concurrent sexual transmitted disease, low socio-economic status and certain racial groups (Amsel *et al.* 1983; Josey & Lambe 1976). These circumstances also have a strong epidemiological association with preterm labour. Given these findings, the identification earlier in pregnancy of women with the microbiological profile of bacterial vaginosis would create an opportunity for therapeutic intervention which, by modification of this profile, might result in a reduction of preterm labour in this group.

The second bacteriological grouping is of enteropharyngeal origin and contains the organisms *Klebsiella* spp., *E. coli, Haemophilus* spp. and *S. aureus*, all of which have clearly identified virulence factors (capsules, haemolysins, resistance to phagocytosis,etc.). These bacteria are associated with PROM, amnionitis, placentitis and systemic signs of inflammation. In the setting of such an invasive form of infection there are many different and connecting pathways that may be activated involving bacterial endotoxin and cytokine release which may result in an increased bioavailability of prostaglandin (Romero *et al.* 1988). Septicaemia (and systemic infection) is clearly an initiator of labour: invasive genital infection may initiate labour via the same mechanisms as systemic infection.

Invasive infection with enteropharyngeal bacteria implies immunological naivety in relation to the particular bacterial strain. If this is so then it would be reasonable to assume that such bacteria were newly acquired just before labour. The introduction to the vagina of enteropharyngeal bacteria might be a direct result of certain sexual practices. Although there is some information linking coitus with amnionitis and preterm labour (Toth *et al.* 1988), no detailed study of sexual behaviour in pregnancy has been reported. We suggest that there is a need for such studies.

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Platelet angiotensin II binding sites in normotensive and hypertensive women

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Summary. Specific binding of angiotensin II (AII) to platelets was measured in 89 women, 25 nulliparous non-pregnant women and 64 primigravida in the third trimester of pregnancy. There was significantly lower binding in the 25 pregnant women who were normotensive (2·3 fmol/10^9 cells) when compared with the non-pregnant women (9·0 fmol/10^9 cells $P<0{\cdot}001$). Significantly higher platelet AII binding levels were found in the 39 women who had pregnancy induced hypertension (PIH) (5·5 fmol/10^9 cells) when compared with the 25 normotensive pregnant women ($P<0{\cdot}001$). Of the 39 women with PIH, platelet AII binding was higher in the 23 women who had pre-eclampsia (7·0 fmol/10^9 cells), when compared with the 16 who had non-proteinuric PIH, (4·6 fmol/10^9 cells) although the difference was not statistically significant ($P<0{\cdot}04$). The pressor response to AII is also diminished in pregnancy, yet less so if pregnancy induced hypertension develops. Platelets may provide a readily accessible tissue with which to study AII responsiveness in pregnancy.

In pregnancy there is progressive diminution in the pressor and renal responsiveness to angiotensin II (AII) (Abdul-Karim & Assali 1961; Gant *et al.* 1973; Broughton Pipkin *et al.* 1982). In women who subsequently develop pregnancy-induced hypertension (PIH), the pressor response is comparatively greater (Talledo *et al.* 1968; Gant *et al.* 1973). Indeed, the pressor response to AII at 28 weeks gestation has been used as a predictive test for PIH (Oney & Kaulhausen 1982; Wallenburg *et al.* 1986). Although far from infallable, it is the most consistently reliable test for predicting PIH. However, it is logistically quite unsuitable for screening the general pregnant population, requiring placement of an intravenous cannula, and taking at least an hour to perform with a clinician in attendance.

Platelets have many of the structural and biochemical characteristics of smooth muscle cells. In response to drugs, similarities between changes in platelet behaviour and changes in vascular tone have been described, with agents that cause vasoconstriciton such as catecholamines, enhancing platelet aggregation (Cameron & Ardlie 1982). Cowley *et al.* (1984) demonstrated a correlation between aspects of platelet behaviour and changes in forearm blood flow in response to cold stimulation, suggesting these factors might ultimately be dependent upon cyclic AMP levels and calcium flux in both the platelet and the blood vessel.

Specific AII binding sites with the characteristics of receptors are present on platelets (Moore & Williams 1981; Ding *et al.* 1984).

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Their Kd is around 10^{-10} mol/l, similar to that described for vascular smooth muscle in animal studies (Gunther *et al.* 1980) and appropriate to circulating plasma AII concentrations. Changes in the renin-angiotensin system consequent upon manipulation of dietary sodium intake evoke parallel changes in platelet and arterial muscle AII receptors (Moore *et al.* 1984; Ding *et al.* 1985). It thus seems possible that a study of platelet AII receptors may reveal them to be a suitable analogue of vascular smooth muscle, thus establishing an *in vitro* test for the sensitivity to AII.

We have therefore measured specific AII binding on platelets from non-pregnant, and from both normotensive and hypertensive women in the third trimester of pregnancy.

Subjects and methods

Eighty-nine women were investigated in a cross-sectional study. Women were recruited randomly from the antenatal clinic, not more than four being recruited on any one day, due to the time taken to perform the assay. Their ages, gestational age and platelet characteristics, are summarized in Table 1. None was known to be suffering from renal, metabolic or cardiovascular disease. All the non-pregnant women were normotensive and nulliparous, samples were obtained between days 5 and 9 of the menstrual cycle. All the pregnant women were in their first pregnancy. Those in the PIH group were all in the third trimester when the assay was performed. Twenty-three had pre-eclampsia (PE). PIH was defined as a blood pressure of ≥140/90 mmHg, occurring on two separate occasions in a previously normotensive primigravida after the 20th week of pregnancy (Davey & MacGillivray 1987), and PE was defined as PIH with the addition of proteinuria (>0·3 g protein/24 h), in the absence of a urinary tract infection. All the women in the other group remained normotensive following investigation and had no clinically detectable proteinuria. None in any group was taking any medication except iron and vitamin supplements. In the PIH group all samples were taken before any anti-hypertensive therapy was given. All subjects had an unrestricted sodium intake and had normal serum urea, creatinine and electrolyte concentrations.

Assay methods

Venepuncture was performed, platelets were prepared and binding sites studied as described previously (Baker *et al.* 1990) using the method described by Ding *et al.* (1984). Plasma AII was measured by radioimmunoassay (Broughton Pipkin & Symonds 1977).

Statistics

Mean (SE) values or medians are quoted as appropriate. Values of binding below 0·5 fmol/10^9 cells were deemed to be below the limit of detection of the assay and have been coded as zero. In comparisons of binding and gestational age and plasma AII, the Mann-Whitney *U*-test was used. In comparisons of serum urate estimations, Student's *t*-test was used. Correlations between binding concentrations and plasma AII levels were assessed using Spearman correlation coefficient for non-normally distributed data. The significance of differences in median binding amongst the groups were analysed using Kruskal-Wallis one-way analysis of variance. To allow for multiple comparisons amongst groups, $P<0·01$ rather than $P<0·05$ was taken as the level indicating significance. Canonical discriminant analysis was performed using the Statistical Package for the Social Sciences (Wilks lambda method, SPSS-X, 1983).

Results

There were no significant differences in the recovery of platelets from whole blood between non-pregnant women (mean 62·5% SE 1·8%), normotensive pregnant women (61·2% SE 1·4%) and women with PIH (59·0% SE 2·4%). Contamination with leucocytes was <1%, 15×10^3/μl), and no erythrocytes were detected.

There was no significant difference in gestational age between the normotensive and the PIH groups (Table 1; $P=0·37$).

The median value of platelet AII binding was 9·0 fmol/10^9 cells (Fig. 1) in the non-pregnant group. There was significantly lower binding in the normotensive group (2·3 fmol/10^9 cells, $P<0·001$). Median platelet AII binding thus fell by 75% in normotensive third trimester pregnancy compared with non-pregnant women. In the 39 women with PIH, the fall from the non-pregnant value was only 39%, with platelet AII binding being significantly greater than in the normotensive third trimester group. (5·5 fmol/10^9 cells, $P<0·001$) (Fig. 1). Platelet

Table 1. Platelet AII binding quantified in 25 nulliparous (non-pregnant) women and 64 women in their first pregnancy

		Third trimester pregnancy			
			Hypertensive		
Variable	Non Pregnant (n=25)	Normotensive (n=25)	Non-proteinuric (n=16)	Proteinuric (n=23)	Total (n=39)
Age (years)					
median (range	26 (20–42)	25 (15–30)	23 (17–31)	25 (19–33)	24 (17–33)
Gestation (weeks)					
mean (SE)	—	33·3 (0·92)	34·9 (0·71)	33·6 (0·83)	34·2 (0·83)
Platelet count (10^3/ml)					
mean (SE)	226 (10)	174 (6)	174 (11)	163 (20)	168 (18)
Mean platelet value (fl)					
mean (SE)	7·8 (0·11)	8·6 (0·21)	9·6 (0·32)	10·1 (0·41)	9·9 (0·40)
Platelet distribution width					
mean (SE)	15·8 (0·32)	17·4 (0·21)	17·8 (0·20)	18·0 (0·31)	17·9 (0·30)

AII binding in the 23 women with pre-eclampsia (7·0 fmol/10^9 cells) was significantly higher than that in the normotensive pregnant women ($P<0·001$) but not when compared with the 16 women with non-proteinuric PIH (4·6 fmol/10^9 cells, $P=0·04$). Platelet AII binding was higher in the women with non-proteinuric PIH than in the normotensive pregnant group although the difference was not statistically significant ($P=0·03$).

The median plasma AII concentration was 6·7 pg/ml in the non-pregnant group. Significantly higher AII levels were found in pregnancy: 19·3 pg/ml ($P<0·01$) in the normotensive group and 21·1 pg/ml ($P<0·01$) in the pre-eclampsia group. In the patients with PIH only, the higher level of AII (16·2 pg/ml) did not differ significantly from that in the non-pregnant group ($P<0·02$). There were no significant differences between any of the pregnant groups. In none of the pregnant groups was there any correlation between platelet AII binding and plasma AII ($P=0·2–0·4$, $r=0·15$ to $+0·25$).

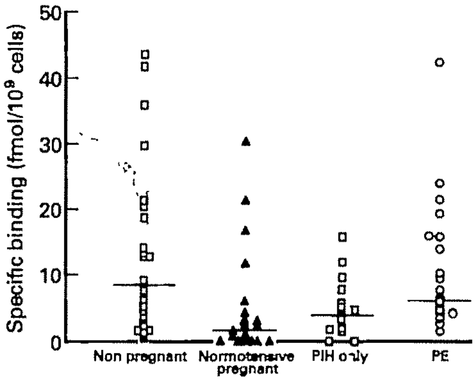

Fig. 1. Platelet AII binding (fmol/10^9 cells), with median values shown of non-pregnant women, normotensive pregnant women in the third trimester, patients with non-proteinuric PIH (PIH only), and patients with pre-eclampsia (PE).

The mean serum urate levels were significantly lower in the normotensive group (209 µmol/l, SE 11) than in the PIH group (335 µmol/l, SE 17) ($P<0·001$). There were no significant differences in the platelet count and the platelet distribution between any of the pregnant groups. Mean platelet volume was significantly higher in the PIH group than in the normotensive group ($P<0·01$).

Discussion

It has been shown previously that the pressor responsiveness to AII is diminished early in pregnancy (Gant *et al.* 1973; Broughton Pipkin *et al.* 1982). The fall of platelet AII binding in early pregnancy (Baker *et al.* 1990) parallels the diminution in pressor response to infused AII, which also occurs early in pregnancy, this being important if the binding studies have screening potential. In PIH the overall pressor response is enhanced; we have shown the same phenomenon in platelet AII binding. Moreover, preliminary results from an ongoing study of AII infusion in pregnancy suggest that platelet AII binding correlates with AII pressor responsiveness (Baker, Broughton Pipkin & Symonds, unpublished work).

We have reported previously that the inverse correlation between plasma AII and platelet AII binding that exists in the non-pregnant state (Moore *et al.* 1984) was not found in normotensive pregnancy (Baker *et al.* 1990). This study suggests that in hypertensive as in normotensive pregnancy, some mechanism other than down-regulation by plasma AII is responsible for changes in platelet AII binding site density.

The markedly elevated levels of binding in the PIH group suggests a possible role for the assay marker, particularly since patients with pre-eclampsia tended to have the higher binding than those with non-proteinuric PIH (Fig. 1). In a multifaceted disease such as PIH one would not expect a total lack of overlap, but these results in the established condition give discrimination between normotensive and hypertensive patients as good as that found using the AII infusion test. Oney & Kaulhausen (1982) found a false positive rate of 55% in European women using the AII infusion test, although the false negative rate was only 5%. The corresponding results for platelet AII binding in this study are a false positive rate of 46% and a false negative rate of 22%. Interestingly, the results of such discriminant analysis are improved if urate estimation and platelet AII binding levels are combined, with false positive and false negative rates of 25% and 17% respectively: 78% of patients being correctly classified.

We have suggested previously (Baker *et al.* 1990) that platelet AII binding sites in pregnancy have very similar affinity and dissociation constants to those found outside pregnancy (Moore & Williams, 1981; Ding *et al.* 1984). Formal comparison of these constants in normal and hypertensive pregnancy cannot be undertaken because of the very low binding in platelets in the normotensive pregnancy. Indeed, we have only been able to measure the dissociation constant (using competitive studies) in five women in the third trimester. These women had high levels of binding (8·0 fmol/10^9 cells) and three of them subsequently developed PIH. Although Scatchard analyses indicated that the binding sites were of high affinity (dissociation constant $2{\cdot}5 \times 10^{-10}$ mol/l), it is difficult to assess whether they are representative of either normotensive or hypertensive pregnancy. In pre-eclampsia, platelet turnover is increased (Rakocki *et al.* 1979). It is possible that platelet turnover *per se* may account for the altered platelet AII binding We plan to investigate this possibility by studying platelet AII binding in individuals before, and after, donation of large volumes of blood.

A prospective longitudinal study of binding in pregnancy has been begun to see if similar patterns are found when a cohort of pregnant women are followed.

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Intrauterine pressures in labours induced by amniotomy and oxytocin or vaginal prostaglandin gel compared with spontaneous labour

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Summary. Uterine activity during the first stage of labour was measured by an intrauterine transducer in 22 women induced with intravaginal PGE2 gel, in 37 induced by amniotomy and intravenous oxytocin, and in nine women in spontaneous labour. The nulliparous women in the PGE2 gel group had a significantly longer pre-established phase of labour and a significantly shorter established phase than nulliparae induced by amniotomy and oxytocin. The mean levels of total uterine activity (kPas) during labour and the uterine activity integrals (kPas/15 min) were significantly lower in nulliparae induced with PGE2 gel than in those induced by amniotomy and oxytocin. These findings suggest that PGE2 gel has a positive, beneficial effect on cervical compliance during the pre-established phase, resulting in less myometrial effort during established labour. These effects were less evident in parous women, probably because of an innate lower cervical resistance due to their previous labours. Uterine activity patterns during the 4 h leading to full cervical dilatation in nulliparae were similar in labours induced with PGE2 gel and spontaneous labours, whereas labours induced by amniotomy and oxytocin exhibited a significantly different pattern. Expulsion of the fetus during normal labour is a function of both uterine contractions and a decrease in the cervical resistance and the data suggest that induction by PGE2 gel more closely mimics spontaneous labour, whereas the predominant effect of oxytocin is to stimulate myometrial activity.

Prostaglandin E2 (PGE2) reduces cervical resistance in a manner which is independent of uterine contractions, while oxytocin has little effect (Calder & Embrey 1973). As a result of this, locally administered PGE2 has proven to be a useful agent for induction of labour, especially when the cervix is unfavourable (Keirse & van Oppen 1989). It has been suggested that, with a favourable cervix, induction of labour with locally administered PGE2 more closely resembles natural labour than induction by amniotomy and oxytocin (Kennedy *et al.* 1982; Turner *et al.* 1988), although this has not been validated quantitatively. This study examines

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Table 1. Characteristics of the three study groups

	Induced labour		
	PGE2 vaginal gel ($n = 43$)	Amniotomy + oxytocin ($n = 41$)	Spontaneous labour ($n = 9$)
Nulliparae	28 (65%)	26 (63%)	7
Multiparae	15 (35%)	15 (38%)	2
Reason for induction			
Post-term	24 (56%)	20 (49%)	-
Hypertension	11 (26%)	9 (22%)	-
Other	8 (18%)	12 (29%)	-
Maternal age (years)	26·2 (4·9)	26·4 (5·4)	24·8 (6·4)
Bishop's score	6·2 (1·4)	6·5 (1·5)	
Gestation (weeks)	40·9 (1·2)	40·7 (1·4)	39·4 (1·0)
Mode of delivery			
Spontaneous	29 (67%)	31 (75%)	9 (100%)
Instrumental	7 (16%)	8 (20%)	0
Abdominal	7 (16%)	2 (5%)	0
No. of live births	43	41	9
No. with Apgar scores >6			
At 1 min	35 (81%)	34 (83%)	7 (80%)
At 5 min	43 (100%)	38 (93%)	9 (100%)
Excluded from UAI analysis			
Incomplete data-set	7	2	
Augumented labour (protocol violation)	7		
?Catheter misplaced	7	2	
Sample too small			2 (parous)

Results are means (SD) or n (%) values as appropriate.

this hypothesis, and uses total uterine activity as an indicator of cervical resistance (Arulkumaran *et al.* 1985).

Subjects and methods

Women in the two induction groups were carrying a singleton, term, cephalic, live, normally formed fetus, and had a modified Bishop's score of at least 4 (Bishop 1964). Women were excluded if they had had a caesarean section previously or if they had had four or more children. A total of 93 women were enrolled in the study, comprising 84 in whom labour was induced and nine who were in spontaneous labour. Using sealed coded envelopes, women who required induction of labour were randomly allocated to be treated either with amniotomy and intravenous oxytocin or with intravaginal PGE2 gel, and the randomization was stratified to ensure similar numbers of nulliparous and parous women in each induction group.

Twenty-six nulliparae and 15 parous women (total 41) were randomized to the oxytocin group. Each of them had a forewater amniotomy before the intra-amniotic insertion of an intrauterine pressure catheter. An intravenous infusion of oxytocin (Syntocinon, Sandoz) 10 units in 0·5 litre dextrose/saline was then set up at an initial dosage of 2 mU/min. This infusion rate was increased at the discretion of the attendant midwife, in variable increments to a maximum of 32 mU/min, or until the midwife judged that there were adequate uterine contractions. A scalp electrode was applied for continuous monitoring of the fetal heart rate.

A total of 43 women (28 nulliparous and 15 parous) were randomized to receive PGE2 gel. An initial dose of 1 mg PGE2 in triacetin gel (Prostin Gel, Upjohn, Crawley, Sussex) was deposited in the posterior vaginal fornix. The intrauterine catheter was introduced extra-amniotically leaving the membranes intact, a validated method of measuring intrauterine pressure (Steer *et al.* 1975). In nulliparae,

Table 2. Characteristics of the women in the three study groups with intrauterine pressure data available for analysis

	Induced labour		
	PGE2 gel (n = 22)	Oxytocin (n = 37)	Spontaneous labour (n = 7)
Nulliparae	12	23	7
Multiparae	10	14	0
Reason for induction			
Post-term	16	18	
Hypertension	3	8	
Other	3	11	
Maternal age (years)			
Range	18-35	18-35	18-33
Mean	25·3	26·1	24·8
Bishop's score			
Range	4- 9	4- 9	
Median	6	6	
Gestation (weeks)			
Range	38-42	38-42	38-41
Mean	40·4	40·7	39·4
No. infants with Apgar scores >6			
At 1 min	20 (91%)	32 (86%)	7 (80%)
At 5 min	22 (100%)	35 (94%)	9 (100%)

vaginal examinations to assess progress were made 4 and 8 h after induction, at which times further doses of 1 mg or 2 mg PGE2 gel were administered, up to a maximum of three doses, depending on the following criteria. If the woman was in established labour (defined for the staff involved in the study as an increase in the frequency, duration, strength and synchronicity of uterine contractions, together with progressive effacement and dilatation of the uterine cervix) no further PGE2 was administered, but an amniotomy was performed. If there had been some progress since the previous dose, without labour being established, a further 1 mg PGE2 gel was administered. In women in whom there had been no progress, 2 mg PGE2 gel was given. Parous women were examined after 6 h for only one additional dose of either

Table 3. Time spent in pre-established and established phases of labour

	Pre-established phase (h)		Established phase (h)	
	PGE 2 gel	Oxytocin	PGE2 gel	Oxytocin
Nulliparae				
No of women	12	23	12	23
Range	2·0–9·0	0·0–3·3	1·5–6·5	1·8–17·25
Mean (SD)	5·6 (2·1)	1·0 (1·0)	3·9 (1·4)	6·5 (3·4)
95% CI	4·4–6·8	0·0–2·0	3·1–4·7	5·1–7·9
P	<0·01		<0·01	
Multiparae				
No of women	10	14	10	14
Range	0·25–4·0	0·25–1·3	1·0–8·3	1·2–11·8
Mean (SD)	1·6 (1·6)	1·1 (0·4)	4·4 (2 2)	4·0 (3·0)
95% CI	0·6–2·6	0·9–1·3	3·0–5·8	2·4–5·6
P	>0·05		>0·05	

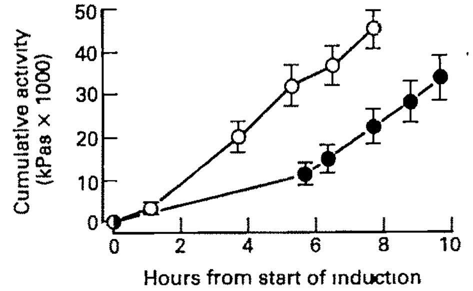

Fig 1. Mean cumulative uterine activity over time during labour in nulliparous women induced with amniotomy and oxytocin ○—○ or by PGE2 gel ●—●.

1 mg or 2 mg PGE2 gel, up to a maximum of two doses, applying the same criteria as for nulliparae. If the women receiving PGE2 gel were not in established labour 12 h after the initial dose of PGE2, labour was augmented with intravenous oxytocin.

In the women in spontaneous labour, the intrauterine catheter was inserted intra-amniotically, after amniotomy, at a stage of labour when they preferred to stay in bed.

Uterine activity was measured using a Gaeltec intrauterine catheter-tip pressure transducer attached to a Sonicaid FM3R fetal monitor, which continually recorded intrauterine pressure in mmHg. Every 15 min the uterine activity integral (UAI) was recorded in kilopascal-seconds (kPas). This is the summation of the active pressure within the uterus over the previous 15 min, and takes into account the frequency, amplitude and duration of each contraction, but does not include resting uterine tone. UAI values were recorded throughout the first stage of labour for the two induction groups, and from the time of catheter insertion to full cervical dilatation in the spontaneous labour group. The established phase of labour was retrospectively defined as the attainment of consistent UAI values of ⩾800 kPas/15 min, as this value corresponds to the 10th centile for the range of uterine activity recorded in spontaneous labour (Steer *et al.* 1984).

UAI data-sets for induced labours, which ended in delivery by caesarean section or required augmentation by more than one agent, have not been analysed. Erroneous intrauterine catheter recordings, possibly due to a misplaced catheter, have also been excluded from the analysis (see Table 1). Thus, the UAI data presented may not be representative of the original randomized groups. SPSSX and Statgraphics software packages were used for data analyses. Statistical significance has been calculated using Student's t, Mann-Whitney U or χ^2 hypothesis tests. Where appropriate 95% confidence intervals are given. Local ethics committee permission and written informed consent was obtained from each woman.

Results

Table 1 compares the three study randomized groups for age, parity, Bishop's score, gestation and obstetric outcome, and Table 2 demonstrates the similarity of the baseline variables for the groups of women whose UAI data were analysed. Table 3 shows that the mean duration of the pre-established phase of labour in nulliparae induced with PGE2 gel was significantly greater than in those induced by amniotomy and oxytocin. Conversely, the duration of the established phase was significantly shorter in the PGE2 group than in the group induced by amniotomy and oxytocin. Figure 1 illustrates the prolonged pre-established phase in nulliparae, induced with PGE2 and shows that, in spite of this, their cumulative uterine activity at all time-

Table 4. Cumulative uterine activity during first stage of induced labour

	Nulliparae		Parous women	
Uterine activity (kPas)	PGE2 gel	Oxytocin	PGE2 gel	Oxytocin
No. of women	12	23	10	14
Range	14873-80059	13106-121779	10292-56331	1118-75758
Mean (SD)	33766 (18150)†	45211 (22096)*†	24742 (14722)	30584 (20418)*
95% CI	23287-44245	35996-54426	15431-34053	19670-41498
P	$<0·05$		$>0·05$	

*Significance of difference between nulliparae and parous women induced by amniotomy and oxytocin $P<0·05$.
†Significance of difference between nulliparae induced by PGE2 gel or amniotomy and oxytocin, $P<0.05$.

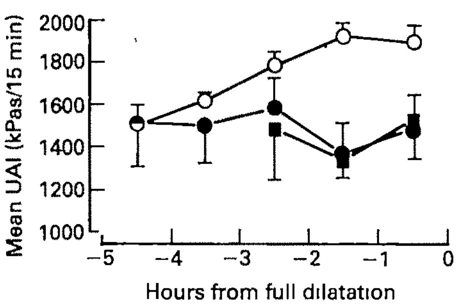

Fig. 2. Mean uterine activity integrals (UAI) during time leading to full cervical dilatation in nulliparous women induced with PGE2 gel (●—●, $n = 12$) or by amniotomy plus oxytocin (○—○, $n = 23$) and in spontaneous labour (■—■, $n = 7$).

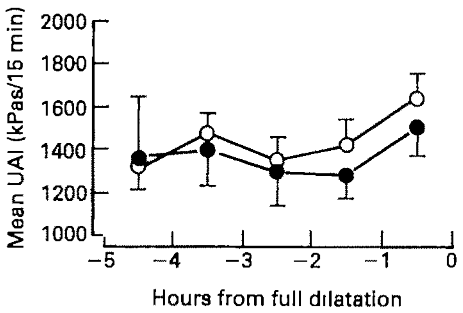

Fig. 3. Mean uterine activity integrals (UAI) during time leading to full cervical dilation in parous women induced with PGE2 gel (●—●, $n = 10$) or by amniotomy and oxytocin (○—○, $n = 14$)

points was lower than in nulliparae induced by amniotomy and oxytocin. The mean total cumulative activity during the first stage of labour was found to be significantly less in nulliparae induced with PGE2 gel than in nulliparae induced by amniotomy and oxytocin (Table 4). There was no significant difference between nulliparous and parous women receiving PGE2 gel, but there was a significant difference between the nulliparae and multiparae induced with oxytocin. Nulliparous women induced with PGE2 gel required significantly less overall uterine activity to attain the same degree of cervical dilatation than women induced with oxytocin.

Figure 2 shows a similar pattern of uterine activity in nulliparae induced with PGE2 gel as in spontaneous labour during the hours leading to full dilatation, with lower UAI values than those observed in nulliparae induced by amniotomy and oxytocin. The difference between the two induction regimens is not evident when a similar comparison is made for parous women (Figure 3).

The mean total dosage of PGE2 gel was 1·8 mg (range 1–3 mg) in nulliparous women, and 1·0 mg in parous women (all 10 requiring only the initial 1 mg dose). Full dilatation was achieved in five of the 12 nulliparae after a single 1 mg dose, and none of the remainder required more than two doses of PGE2 gel. The mean maximum infusion rate of oxytocin was 16.4 mU/min (range 4–32 mU/min) in nulliparae, and 13·4 mU/min (range 4–32 mU/min) in parous women. The maximum permitted rate of 32 mU/min was used in only four nulliparous women and one parous woman, whereas 10 (41%) nulliparae achieved full dilatation at an infusion rate of 12 mU/min or less.

Discussion

The intention of this study was to perform a randomized, controlled trial. Women were randomly allocated to their method of induction, although it was not possible to use a 'blind' technique. Other biases occurred because of the exclusion from the analysis of the UAI data-sets of those women who had an amniotomy at the wrong time, and of those who were delivered by caesarean section before full dilatation. However, uterine activity was recorded objectively, using continuous data measurement, and it is not thought that these known biases significantly affect the findings of the study.

Oxytocin is a potent stimulator of myometrial contractions but has little effect on the cervix, presumably because of the low numbers of oxytocin receptors in the cervix compared with the increasing numbers in the myometrium and decidua as pregnancy progresses (Fuchs *et al.* 1982). Prostaglandins, however, not only induce uterine contractions (Karim *et al.* 1970), but also cause an increase in compliance, and hence a decrease in the resistance of the uterine cervix (Bryman *et al.* 1986).

Arulkumaran *et al.* (1985) suggested that the total uterine activity throughout oxytocin-induced labour is indicative of the degree of cervical and pelvic tissue resistance. In our study, the lower levels of uterine activity experienced by nulliparae induced with PGE2, compared with those who received oxytocin, may be explained by a reduction of cervical resistance induced by PGE2. It is likely that this softening of the cervix started during the pre-established phase of labour when uterine activity was at a relatively low level. This theory is reinforced by the fact that nulliparae receiving PGE2 gel required less uterine effort than those in the oxytocin group to achieve the same degree of cervical dilatation during the established phase. These differences between induction agents were significant only in nulliparous women, since parous women already have a reduced cervical resistance as a result of their previous labours (Turnbull 1957), and are known to require less uterine effort during both spontaneous and induced labour to effect vaginal delivery (Seitchik *et al.* 1983; Arulkumaran *et al.* 1984 & 1985; Steer *et al.* 1985).

The mean maximum infusion rate of oxytocin was 16.4 mU/min, and the maximum permitted rate of 32 mU/min was necessary in only a few women. Arulkumaran *et al.* (1985) showed that the total uterine activity during the first stage of labour is independent of the dose of oxytocin, lower doses are associated with lower UAI, but tend to be compensated for by a longer labour so that the total uterine effort in women of similar parity and Bishop score is usually the same. Thus, it is unlikely that lower infusion rates of oxytocin in our study would have reduced the mean total cumulative uterine activity in the amniotomy and oxytocin group.

When the mean UAI are plotted against the hours leading to full dilatation in nulliparous women (Fig. 2), the levels in spontaneous labour closely resemble those in labours induced with PGE2 gel, but differ significantly from the pattern seen in oxytocin-induced labour. This suggests that nulliparae in spontaneous labour also experience a pre-established phase, similar to that observed in nulliparae induced with PGE2, during which there may be a reduction in cervical resistance with relatively little uterine activity. This unseen maturation of the cervix probably shortens the duration of the established phase of labour and reduces the total uterine effort required to effect delivery. The pre-established phase of labour is virtually absent during oxytocin inductions, leaving the myometrium to contract against a resistant cervix. Our data also support the claim that labour induced with prostaglandins is as efficient, if not more so, than the traditional method of amniotomy and oxytocin, especially where the cervix is unfavourable (Calder & Embrey 1973). PGE2 gel may also be safer than oxytocin for the induction of labour after a previous caesarean section (Mackenzie *et al.* 1984), since the uterus does not have to contract as strongly to achieve the same degree of cervical dilatation.

Conclusion

In nulliparae with a favourable cervix who required induction of labour, intravaginal PGE2 gel produced a pattern of uterine activity which more closely resembled that of spontaneous labour compared with labour induced with amniotomy and oxytocin. This is probably because PGE2 acts both on the myometrium to induce contractions, and on the uterine cervix to reduce resistance to the passage of the fetus. The dual effects of PGE2 were less obvious in parous women, who tend to have inherently less cervical resistance because of their previous labours.

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Placental abruption. A case-control investigation

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Summary. The course of pregnancy and labour, neonatal outcome and social circumstances, were compared between 87 women with placental abruption and a control group of 5697 women. First and second trimester haemorrhage, amniocentesis, congenital malformations, maternal smoking and a job involving much standing or walking were associated with placental abruption.

In an investigation of 5727 pregnancies and deliveries, it was found that both employment as sales assistant during pregnancy and pre-eclampsia were significantly associated with placental abruption (Wohlert 1989). As that study included only 30 women, it was decided to collect a larger series from the same area and to use the case-control technique.

The purpose of the present study was to investigate the significance of various risk factors and the effect of employment during pregnancy on the occurrence of placental abruption.

Subjects and methods

The data analysed are part of a current investigation of the influence of environmental factors on pregnancy, delivery and the newborn (Neilsen *et al.* 1982). During the period 1.12.80 to 31.12.82, a total of 5727 singleton deliveries was recorded. They fulfilled the following criteria: the mother was a resident of a central city (Århus, Denmark) or two surburban areas, the gestational age was at least 28 completed weeks and the birthweight was ⩾1000 g. These criteria included 95% of all deliveries from the area, and 30 of them were complicated by placental abruption (Wohlert 1989). The remaining 5697 pregnancies formed the control group. In the following 3 years an additional 57 pregnancies with placental abruption were registered, all fulfilling the above criteria Thus the cases in the present study are 87 pregnancies complicated by placental abruption.

The data in the study were obtained from the hospital records, and from a questionnaire, which was handed out to the pregnant woman at approximately 29 weeks gestation, and collected just before delivery.

The diagnosis of abruption of a normally implanted placenta was based on the clinical features of haemorrhage, a tender, hypertonic uterus and the observation of a retroplacental clot and/or depression of the underlying placental tissue. Thus pregnancies with minor abruption of the placental margin were not included.

The WHO (1977) definition of perinatal mortality was used. The infants were termed small-for-gestational age (SGA) if the birthweight was <10th centile according to the local, sex-specific birthweight-for-gestational-age chart (Wohlert 1989). The diagnosis of pre-eclampsia was based on the observation of elevated blood pressure

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(≥140/90 mmHg) on at least two independent occasions in the third trimester and proteinuria, provided there had been no previous hypertensive disorder. Pregnancy-induced hypertension was defined as the development of hypertension (≥140/90 mmHg) in the third trimester without proteinuria, again, provided there had been no previous hypertensive disorder.

Social status was defined, using national criteria, with class I as the highest group. The classification was based on the woman's or her partner's occupation and the higher class of the two was used to describe social class during pregnancy. As a primary attempt to investigate the hypothesis that work involving pronounced standing or walking increased the risk of placental abruption, a special 'exposure' group was used. Typical occupations in this group were nurses, nursing aides, sales women and hairdressers. This classification was derived from the woman's occupation during pregnancy and her description of her job. These classifications were made before the data were analysed (Wohlert 1989).

The association between the risk of placental abruption and some of the maternal, fetal and pregnancy-related factors was estimated by the use of crude univariate analyses including odds ratios with 95% confidence intervals (CI) and χ^2 values. For further analysis, a logistic regression model was built up, which allowed the simultaneous control of possible confounding variables (Breslow & Day 1980). All variables listed in Table 1 were included in the model. After stepwise selection a final model was obtained (Table 2). All variables were coded as categorial variables: a reference value of zero indicated that the factor was absent. Age below 20 years and social class I were chosen as reference categories. No smoking was used as the reference category in relation to smoking and uncertain smoking. Information about smoking was recorded as a dichotomous variable, but could be obtained only from a part of the study population. Consequently category of uncertain smoking was created, in order to avoid the exclusion of too many cases from the analyses.

Results

The prevalence of placental abruption was 0·5%

Table 1. Crude univariate association between certain risk factors and placental abruption

Risk factor	Cases (n = 87)	Controls (n = 5697)	Odds ratio	(95% CI)	χ^2
Nulliparae	46 (53%)	2898 (51%)	1·0	—	0·1
Age (years)					5·9
<20	1 (1%)	396 (7%)	0·1	(0·0–0·6)	df = 2
20–29	60 (69%)	3981 (70%)	1·0	—	
>30	26 (30%)	1320 (23%)	1·3	(1·1–1·6)	
Social class					13·9
I	13 (15%)	717 (13%)	1·2	(1·1–1·3)	df = 4
II	5 (6%)	752 (13%)	0·5	(0·3–0·8)	
III	17 (20%)	1217 (21%)	1·0	—	
IV	33 (38%)	1599 (28%)	1·4	(1·2–1·7)	
V	19 (22%)	1412 (25%)	0·9	(0·9–1·0)	
Standing at work	28 (32%)	1313 (23%)	1·4	(1·0–1·9)	4·0
Smoking					45·3
No	12 (14%)	2243 (39%)	0·4	(0·3–0·5)	df = 2
Yes	25 (29%)	1939 (34%)	0·9	(0·9–0·9)	
Uncertain	50 (58%)	1515 (27%)	2·1	(1·7–2·6)	
Congenital malformation	7 (8%)	183 (3%)	2·7	(1·2–5·9)	6·3
Amniocentesis	10 (12%)	300 (5%)	2·4	(1·1–5·0)	5·4
SGA infant	6 (7%)	592 (10%)	0·7	(0·4–1·4)	1·1
Pre-eclampsia	3 (3%)	70 (19%)	2·8	(1·1–8·4)	3·4
Haemorrhage					
First trimester	8 (9%)	188 (3%)	3·0	(1·4–6·7)	7·3
Second trimester	9 (10%)	189 (3%)	3·3	(1·6–6·7)	10·8

CI confidence interval.

Table 2. Association between certain risk factors and risk of placental abruption. Adjusted odds ratio with 95% confidence interval (CI) using logistic regression analysis

	Beta	Odds ratio	95% CI	χ^2
Haemorrhage in				
1st trimester	1·2	3·4	(1·6–7·5)	9·3
2nd trimester	1·1	3·0	(1·4–6·2)	8·8
Amniocentesis	0·7	2·1	(1·1–4·1)	4·6
Congenital malformation	0·8	2·2	(1·0–4·9)	3·8
Standing at work	0·4	1·6	(1·0–2·6)	3·6
Smoking				
No		1·0		
Yes	0·9	2·5	(1·2–5·1)	6·4
Uncertain	1·9	6·5	(3·4–12·3)	33·0

Constant = −5·6.

as 30 cases occurred during the control period 1.12.80 to 31.12.82.

The perinatal mortality rate in the case group was 19·5% and 54% had a preterm delivery. Among the controls the corresponding figures were 0·9% and 3·7%. The frequency of caesarean section was 50·6% in the cases and 6·8% in the controls. The proportion of women working was 74·7% and 73·2%, respectively.

Table 1 shows the results of the univariate analyses. Haemorrhage in the first and second trimester was significantly associated with placental abruption. Thus, about 10% of cases had vaginal bleeding in the first or second trimester compared with about 3% of controls. In addition, second trimester amniocentesis, maternal smoking, congenital malformation and employment involving much standing or walking carried a significantly elevated risk of abruption. The age and social group distribution differed significantly between cases and controls. Parity did not seem to influence the risk. Pregnancies complicated by pre-eclampsia or those resulting in SGA infants did not have an elevated risk of placental abruption.

In the final logistic regression model, only haemorrhage in the first and second trimester, amniocentesis in the second trimester, congenital malformation, employment involving standing or walking, and smoking were associated with an increased risk of placental abruption (Table 2). The category of uncertain smoking was associated with a higher risk than certain smoking.

Haemorrhage earlier in pregnancy could, theoretically, represent minor episodes of placental abruption. Including this variable in the model could reduce the strength of the association between other variables and placental abruption. However, logistic regression models omitting haemorrhage do not affect the results of the analysis.

A history of abortion or of miscarriage was not associated with an increased risk of placental abruption. None of the cases was recorded as having pregnancy-induced hypertension or essential hypertension. The frequency of external version for breech presentation was not significantly different between the two groups. In the case group, the women who had a job involving much standing or walking had a significantly increased risk of perinatal death compared with the other women in the case group, but there was no significant difference in the frequency of preterm delivery.

Discussion

The prevalence of placental abruption varies in different studies from 0·42 to 1·16% and the associated perinatal mortality rates from 21% to 55% (Krohn *et al.* 1987; Blair 1973). These variations could be explained by the lack of uniformity of the definition of placental abruption, different socio-economic conditions in the population investigated, or the fact that hospital data often consist of selected patient groups. The perinatal mortality rate can be lowered by intensive fetal monitoring and readiness to deliver by caesarean section (Lunan 1973). The prevalence of placental abruption, the perinatal mortality rate and the caesarean section rate in the present study are comparable to the results reported by Krohn *et al.* (1987). An association between threatened miscarriage and placental abruption has been reported (South & Naldrett 1973) and our results support the view that vaginal bleeding in the first and second trimester is associated with an increased risk of abruption later in pregnancy.

Second trimester amniocentesis has been reported to be a predisposing factor for abruption (MRC Working Party Report 1978), but this relation could not be demonstrated by others (Tabor *et al.* 1986). Our findings show a significantly increased risk of abruption after amniocentesis but this is based on a rather small number of cases. All amniocentesises were performed under ultrasound guidance. The occurrence of blood stained amniotic fluid was not recorded.

The relation between abruption and hypertension or pre-eclampsia has been disputed. Some investigators have described a correlation (Paintin 1962; Pritchard 1970), whereas others found no correlation (Hibbard 1962; Paterson 1979). None of the women in our case group had pregnancy-induced hypertension or essential hypertension but there was a non-significant increase in the prevalence of pre-eclampsia.

The influence of maternal smoking was difficult to interpret, since information about smoking habits was lacking for a large proportion of the women. The category of uncertain smoking carried a significantly higher risk than certain smoking, suggesting that some heavy smokers may have been concealed in this category. Maternal smoking as a risk factor for abruption has been reported by Naeye (1980), who also reported an association with SGA infants. This was thought to be due to necrosis of the decidua basalis and large placental infarcts (Naeye *et al.* 1977). In the present study placental infarction was not recorded, but SGA infants were not more frequent in the case group. Congenital malformation occurred significantly more often in the case group (8·0% *vs* 3·2%). Similar findings have been reported by other investigators (Hibbard & Jeffcoate 1966; Paterson 1979).

Women whose job was associated with much standing or walking had a significantly increased risk of placental abruption in the univariate analysis and in the logistic regression analysis the increased risk was almost significant. This observation has not been reported previously, but the result provides some support for the earlier findings by De Valera (1968) on the significance of socio-economic status. Compared with the rest of the women in the case group, those women with jobs involving much standing or walking had a significantly increased perinatal mortality rate. There was no difference in gestational age between these subdivisions of the cases indicating that abruption was more severe in this group. The classification of occupation as involving standing or walking was not very strict. Some of the women in this group may not have had a job involving much standing or walking and vice versa. However, this would tend to minimize the difference in risk so that the odds ratio would be underestimated. Further studies concerning the relation between work conditions and placental abruption are called for. Maternal age and parity as risk factors for abruption have been reported in earlier studies, but this has not been confirmed in more recent studies (Krohn *et al.* 1987). Our results are in accordance with the latter, although women above 30 years of age in the univariate analysis carried a significantly increased risk.

It has been suggested that women whose reproductive performance is poor are more likely than the average to experience abruption (Hibbard & Jeffcoate 1966; Paterson 1979). Within the limitations of our study we did not confirm this.

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Maternal and fetal haemodynamics in hypertensive pregnancies during maternal treatment with intravenous hydralazine or labetalol

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Summary. Intravenous treatment with 10 mg of hydralazine or 100 mg of labetalol was randomly allocated to 30 hypertensive pregnant women. Umbilical artery flow velocity waveforms were recorded using a pulsed Doppler duplex scanner (ATL Mk V) and umbilical artery pulsatility index (PI) and fetal heart rate (FHR) were derived from these recordings. Maternal blood pressure decreased significantly after both drugs. Maternal pulse rate increased after hydralazine but did not change significantly after labetalol. FHR did not change significantly after hydralazine but decreased after labetalol. PI decreased after hydralazine and increased after labetalol—most fetuses showed little change but a few in each group showed large changes in PI, as did two of five additional patients studied. We attributed the decrease in PI in some fetuses after hydralazine to vasodilation, and the increase in PI in some fetuses after labetalol to vasoconstriction in the fetoplacental circulation, suggesting that fetal beta-blockade may occur after maternal treatment with labetalol.

Hydralazine, a peripheral vasodilator, has been the most commonly used antihypertensive agent in pre-eclampsia and eclampsia (Chamberlain *et al.* 1978; Chesley 1981). Labetalol hydrochloride, a non-selective beta-blocking agent with post-synaptic alpha$_1$ antagonist and partial beta$_2$ agonist activity, is a newer alternative drug, and both oral and intravenous labetalol compare favourably with intramuscular or intravenous hydralazine in the treatment of acute hypertension during pregnancy (Walker *et al* 1983; Mabie *et al.* 1987). Drugs given to treat maternal hypertension may also affect the fetus, and it is now possible to study the human fetal cardiovascular system non-invasively using Doppler ultrasound

The aim of the present study was to investigate with pulsed Doppler ultrasound, whether a single intravenous dose of either hydralazine, 10 mg, or labetalol, 100 mg, given to treat maternal hypertension, was associated with any detectable changes in fetal heart rate (FHR) or in umbilical artery flow velocity waveform (FVW) characteristics.

Subjects and methods

The study was approved by the university ethics committee. The women were studied at the Royal Maternity Hospital, a regional referral hospital with a special interest in high-risk preg-

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nancy. Thirty women with singleton pregnancies, who were not in labour and had not received any previous antihypertensive therapy, participated in the study after giving informed consent. Ten of them were referred from other hospitals. Hypertension was defined as a blood pressure ≥140/90 mm Hg. The decision to give antihypertensive treatment was made by an independent clinician and was based on assessment of the patient and usually because of acutely elevated or labile blood pressure which did not respond to bed rest. Most women had clinically significant non-infective proteinuria and many had headaches, visual symptoms or hyper-reflexia. These 30 patients were randomly allocated to receive a single intravenous injection of either 10 mg hydralazine or 100 mg labetalol. Randomization was by sequentially numbered sealed envelopes which were opened during the 30-min pre-treatment observation period. There were no statistically significant differences between the two groups in maternal characteristics, fetal outcome (Table 1), or in pre-treatment haemodynamic variables. There was one intrauterine death and one neonatal death in the hydralazine group and one neonatal death in the labetalol group. These deaths were not associated with the drug studies.

We also studied five other patients who were not eligible for randomization. (The data from these five patients were not used in the statistical analyses). One patient with severe pre-eclampsia at 30 weeks gestation, already on oral labetalol therapy, was given 10 mg of intravenous hydralazine. Four patients with deteriorating chronic hypertension, for whom intravenous hydralazine would have been inappropriate, agreed to have their initial dose of labetalol (100 mg) intravenously.

The 3 MHz transducer of a range-gated pulsed Doppler duplex sector scanner with on-line Fast Fourier Transform spectral analysis (Advanced Technology Laboratories) was used to record umbilical artery flow velocity waveforms (FVWs). The method has been described elsewhere (Erskine & Ritchie 1985). The highpass filter was set at 100 Hz. The sample volume was fixed (2 × 4 mm). Five consecutive FVWs of good quality, representing the maximum Doppler shifts obtainable and recorded during fetal apnoea, were selected for subsequent analysis. The pulsatility index (PI) (peak velocity-end diastolic velocity/mean velocity) was used (Gosling & King 1975). The FVWs were measured using the digitizing tablet of a Cardio 80 minicomputer (Kontron Ltd). The FHR was calculated from the FVWs.

Maternal pulse and blood pressure were measured using a DINAMAP Vital Signs Monitor (Critikon Ltd, Ascot, Berks).

Observations of maternal systolic, diastolic and mean arterial blood pressures, maternal pulse rate, and recordings of umbilical artery FVWs were made at 30 min, 15 min and just before (except FVWs) the intravenous injection over 3 min of the antihypertensive drug and then at 5, 10, 20, 30, 45, 60, 90 and 120 min after the start of drug administration. All observations were made with the patient resting comfortably in a semi-recumbent position to avoid supine hypotension.

Statistical analysis

Independent samples *t*-tests were used to test for differences in patient characteristics, fetal outcome, and pretreatment haemodynamic variables. Measurements taken during the 30-min pretreatment control period were averaged to give baseline values for each variable. Results were log transformed where appropriate, and differences in the variables studied were analyzed using repeated measures analysis of variance. The mean values of each variable in the post-treatment period were compared with the mean value in the pre-treatment period using Dunnett's *t*-test at 5% level of significance.

Results

Maternal blood pressure decreased significantly after hydralazine (systolic BP, $P=0{\cdot}003$; mean arterial blood pressure (MAP), $P<0{\cdot}001$; diastolic BP, $P<0{\cdot}001$) and after labetalol (systolic BP, $P<0{\cdot}001$; MAP, $P<0{\cdot}001$; diastolic BP, $P<0{\cdot}001$). Systolic BP ($P=0{\cdot}014$) and MAP ($P=0{\cdot}030$) changes differed significantly between hydralazine and labetalol, but changes in diastolic BP did not reach significance ($P=0{\cdot}052$). Figure 1 shows that the decreases in systolic BP and MAP were smaller after hydralazine than after labetalol.

Maternal pulse rate increased after hydralazine ($P<0{\cdot}001$) but no change occurred after labetalol ($P=0{\cdot}73$) (Fig. 2).

Eight women experienced minor side effects (flushing, light head, nausea) after hydralazine, and six experienced transient scalp tingling, light

Table 1. Maternal characteristics and fetal outcome in 30 hypertensive women treated with hydralazine or labetalol

	Hydralazine (*n*=15)			Labetalol (*n*=15)		
	Mean	(SD)	(range)	Mean	(SD)	(range)
Maternal age (years)	25·9	(6·3)	(20–38)	28·1	(6·2)	(20–40)
No. of primigravida		9			10	
Gestational age at study (weeks)	31·2	(3·2)	(24–36)	32·1	(3·1)	(26–38)
Study-delivery interval (weeks)	2·5	(3·1)	(0·1–11)	1·5	(1·9)	(0·1–6·4)
Median		1·0			0·7	
Gestational age at delivery (weeks)	33·7	(3·3)	(27–39)	33·8	(3·4)	(29–41)
No. of caesarean sections		9			9	
Birthweight (g)	1898	(962)	(840–3965)	1833	(845)	(656–3575)
Median		1670			1750	
Small for gestational age (<3rd centile)		8 (5)			10 (6)	

head or flushing during or shortly after labetalol injection.

There was no significant change in fetal heart rate after hydralazine (*P*=0·89) (Fig. 2). Although FHR decreased significantly after labetalol (*P*<0·001), it remained within the normal range and there were no episodes of bradycardia.

Umbilical artery PI decreased after hydralazine (*P*=0·012), whereas PI increased after labetalol (*P*<0·001) (Fig. 3).

Statistical analysis of PI was complicated by the presence of two obviously different (discordant) umbilical artery FVWs in two patients in the hydralazine group and in one patient in the labetalol group and the emergence of discordant umbilical artery FVWs 30 min after labetalol administration in another patient. Further analysis of PI excluding these four patients showed similar trends to the first analysis although changes after hydralazine were not significant and after labetalol the increase in PI only reached statistical significance at +120 min, compared with from +30 min for all 15 subjects.

These four patients along with one other patient in the hydralazine group and two other patients in the labetalol group showed large changes in PI after the drugs, compared with the remainder who showed little individual change in PI after treatment.

Two of the five patients ineligible for random-

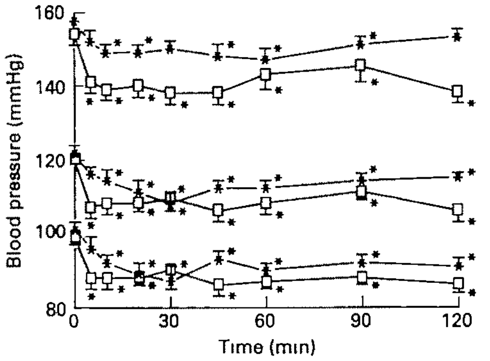

Fig. 1. Mean (± SE) of maternal systolic (top), mean arterial (middle) and diastolic (bottom) blood pressures after 10 mg of hydralazine in 15 patients (×——×) or 100 mg of labetalol in 15 patients (□——□)
*Denotes significant difference from baseline *P*<0·05

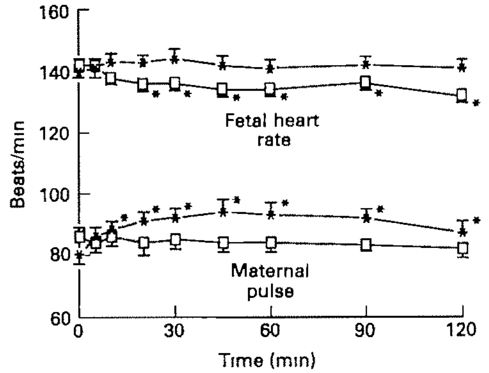

Fig. 2. Mean (± SE) of maternal pulse rate and fetal heart rate after 10 mg of hydralazine in 15 patients (×——×) or 100 mg of labetalol in 15 patients (□——□).
*Denotes significant difference from baseline *P*<0·05.

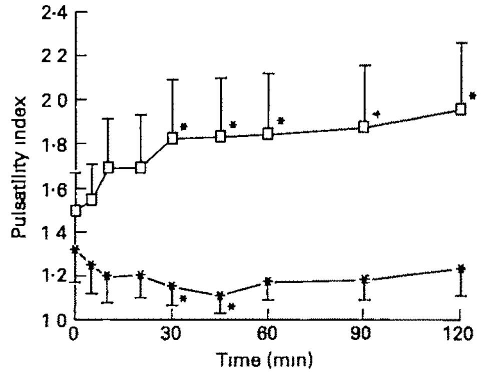

Fig. 3. Mean (± SE) of umbilical artery pulsatility index (PI) after 10 mg of hydralazine in 15 patients (×——×) or 100 mg of labetalol in 15 patients (□——□).
*Denotes significant difference from baseline $P<0{\cdot}05$

ization showed large changes in PI after treatment. One patient with hypertension secondary to renal tuberculosis received 100 mg of labetalol intravenously at 13 weeks gestation before commencing long-term oral labetalol. There was a large increase in the PI value after labetalol and waveform characteristics changed from continuous forward diastolic flow velocities to absence of diastolic flow velocities. She was delivered of a small-for-dates male infant (1105 g) by caesarean section at 31 weeks gestation and the baby did well. Another patient, already receiving oral labetalol therapy, was given hydralazine, 10 mg intravenously, because of deteriorating pre-eclampsia at 30 weeks gestation. Reversed end diastolic velocities easily detected in the umbilical artery FVWs during the control period disappeared within 5 min of hydralazine administration and could not be detected until +120 min when they were once again easily observed. A 656 g male infant, born by caesarean section 2 days later, died from respiratory failure aged 6 weeks. No change occurred in umbilical artery PI after 100 mg labetalol intravenously in the other three patients, all of whom had normal babies at 38 weeks gestation.

Discussion

Antihypertensive drugs used during pregnancy have the potential to affect the fetus, either by altering uteroplacental perfusion or by crossing the placental barrier and affecting the fetus directly. Uteroplacenal blood flow is often decreased in hypertensive pregnancy (Lunell *et al.* 1984) and so it is important to avoid using drugs which might reduce it still further. Labetalol and dihydralazine (which is closely related to hydralazine) do not reduce uteroplacental blood flow (Lunell *et al.* 1982; 1983; Jouppila *et al.* 1985; 1986)) although fetal distress associated with large or sudden decreases in maternal blood pressure after intravenous dihydralazine or hydralazine has been reported (Vink *et al.* 1980; Spinnato *et al.* 1986).

In this study, both hydralazine and labetalol controlled maternal blood pressure smoothly, effectively and without hypotension. Minor side-effects occurred but were usually transient and, in general, both drugs were well tolerated. However, labetalol was more effective than hydralazine in controlling systolic BP and MAP

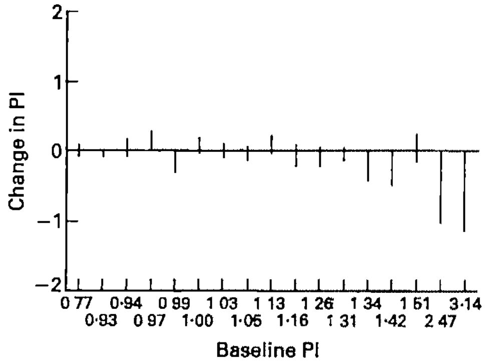

Fig. 4. Maximum changes in pulsatility index (PI) from baseline PI after maternal administration of 10 mg of hydralazine in each of the 15 fetuses (including two fetuses with discordant umbilical arteries).

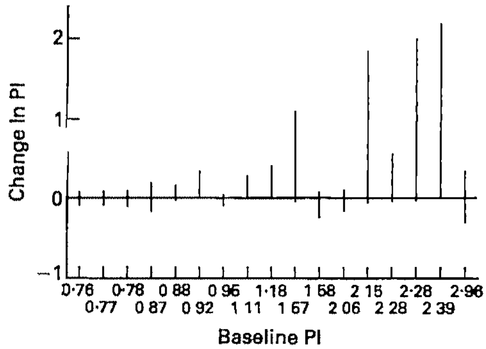

Fig. 5. Maximum changes in PI from baseline PI after maternal administration of 100 mg of labetalol in each of the 15 fetuses (including two fetuses with discordant umbilical arteries).

and had no effect on maternal heart rate, whereas hydralazine caused tachycardia and sometimes palpitations.

In the adult, hydralazine-mediated arteriolar vasodilation causes sympathetic stimulation resulting in tachycardia. Although hydralazine readily crosses the placenta (Liedholm *et al.* 1982), there was no change in fetal heart rate after hydralazine in the present study. This agrees with other studies in which hydralazine in sheep (Ladner *et al* 1970; Ring *et al.* 1977) and dihydralazine in human pregnancy (Lunell *et al.* 1983; Jouppila *et al.* 1985; Ashe *et al.* 1987) did not affect fetal heart rate.

Labetalol also crosses the placenta and fetal concentrations may approach maternal plasma concentrations (Michael 1979; Lardoux *et al* 1983). In the present study the fetal heart rate always remained within the normal range. This agrees with other studies (Lunell *et al.* 1982; Walker *et al.* 1982; Lardoux *et al.* 1983; Jouppila *et al.* 1986; Mabie *et al.* 1987). Nevertheless, in our study, there was a significant decrease in mean fetal heart rate after labetalol, suggesting that some degree of beta-blockade occurred.

Umbilical artery PI increased after labetalol and decreased after hydralazine. In most fetuses the changes in PI after maternal drug treatment were quite small and were at least partly within the error of the technique. In a preliminary study, we found the within-subject coefficient of variation for umbilical artery PI measured repetitively over 2 h to be 6·8%. Normal umbilical artery Doppler FVWs have a biphasic velocity profile with forward flow velocities throughout diastole consistent with low resistance in the umbilical-placental circulation. This extensive vascular bed will dampen any circulatory changes due to vasoactive drugs such as hydralazine or labetalol. This explains why there was little change in PI in most of the fetuses.

The fetuses that showed large changes in PI values after treatment tended to have high baseline PI values, usually more than 2 SD above the mean for gestational age, although not all the fetuses with abnormally high PI values showed large changes in PI after maternal drug treatment (Figs 4 and 5). It is generally agreed that high PI values reflect increased downstream resistance to blood flow. If the placental circulation has a higher vascular resistance than normal it might be more sensitive to cardiovascular changes and this could explain why very marked changes in umbilical artery diastolic flow velocities were observed in some fetuses after maternal drug treatment.

Hydralazine reduces peripheral vascular resistance and systemic blood pressure through relaxation of precapillary arterioles. In hypertensive pregnancies where most fetuses were growth-retarded, Jouppila *et al.* (1985) found that maternal intravenous dihydralazine increased umbilical vein blood flow independently of changes in maternal heart rate, blood pressure, or intervillous blood flow, suggesting that vasodilation occurred in the umbilical vessels. The most likely explanation for the decrease in umbilical artery PI values after hydralazine in our study is that vasodilation occurred within the placental circulation, decreasing resistance and allowing increased blood velocities in diastole.

Umbilical artery PI increased markedly in some fetuses after labetalol, suggesting that placental vascular resistance increased. When given intravenously, the predominant action of labetalol is non-selective beta-blockade (Richards *et al.* 1977). Although the umbilical arteries have no automatic innervation beyond the proximal few centimetres of the umbilical cord (Walker 1984), the umbilical vessels and the placenta are rich in alpha- and, predominantly, beta-adrenoceptors (Dyer 1970; Milligan *et al.* 1986). In sheep, alpha-blockade has no effect on umbilical blood flow (Oakes *et al.* 1980) but beta-blockade is associated with a significant reduction in umbilical blood flow (Oakes *et al.* 1976), particularly in the presence of hypoxaemia (Cohn *et al.* 1982). It seems likely that labetalol-mediated vasoconstriction, possibly superimposed on an already abnormal placental circulation, could explain the observed changes in umbilical artery FVWs after labetalol.

As far as we are aware, there are two other studies of human fetal haemodynamics after labetalol. Jouppila *et al* (1986) found no changes in umbilical vein or fetal descending aortic blood flow or in PI in the fetal descending aorta in 13 fetuses (6 of whom had birthweights <10th centile) in pre-eclamptic pregnancies after maternal labetalol infusion, although the observation period (45 min) may not have been long enough to detect the development of significant changes. Rasmussen (1987) found no significant change in umbilical vein or fetal descending aortic blood flow but an improvement in descending aortic PI in nine fetuses, including seven with previously abnormal PI values, after some days of treatment with oral labetalol, alpha-methyldopa, and plasma expanders. However, the multiple treatment regimen and the differing regulatory mechanisms of the fetal systemic and umbilical circulations make direct comparisons with the present study impossible.

Our results suggest that labetalol may cause beta-blockade in the fetus. This may not matter in the healthy fetus but may be important in the stressed fetus who relies on increased autonomic activity, catecholamine secretion, and circulatory redistribution to maintain blood flow to vital organs (Barrett *et al.* 1972; Cohn *et al.* 1974; Llanos *et al.* 1980; Wladimiroff *et al.* 1986). Animal studies have shown that beta-blockers interfere with the normal fetal cardiovascular responses to stress (Cohn *et al.* 1982; Cottle *et al.* 1983). Although labetalol has not, in general, been associated with adverse fetal effects, clinically significant adrenergic blockade in newborn infants has been reported (Garden *et al.* 1982; Woods & Malan 1983; Haraldsson & Geven 1989). Our studies may suggest that labetalol should only be used with caution to treat maternal hypertension if fetal compromise is suspected. The results of the study also indicate that the possible effects of antihypertensive drugs should be taken into account when interpreting Doppler studies of the fetal circulation, particularly when the findings lie outside the normal range.

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The crown-rump length in early human pregnancy: a reappraisal

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Summary. The crown-rump length (CRL) was measured by means of transvaginal sonography in 41 pregnancies resulting from in-vitro fertilization (IVF). The embryonic CRL could be determined as early as 25 days after follicle aspiration. A reference chart was constructed relating the CRL to the number of days following follicle aspiration. Comparison with the CRL chart by Robinson & Fleming (1975) currently in use revealed that transvaginal sonography allows earlier and more accurate measurement of embryonic CRL.

The reference curve currently in use for crown-rump length (CRL) measurements was derived from data collected with compound B-scan equipment (Robinson 1973; Robinson & Fleming 1975). Transvaginal sonography, with its high resolution imaging, might enable more accurate measurement of the CRL at an earlier stage of pregnancy.

The object of the present study was to establish whether transvaginal measurement of CRL could provide a more accurate reference chart for this dimension.

Subjects and methods

Forty-one women who were pregnant following in-vitro fertilization (IVF) agreed to participate in the study. The IVF procedure provides exact information on the time of ovulation and embryo transfer, and therefore the duration of pregnancy. The study was approved by the local ethics review committee. Mean maternal age was 34 years (range 24–40 years). A pilot study in 23 women showed that the CRL could not be measured until day 25 after follicle aspiration. Therefore, CRL measurements commenced on day 25 in the present study. CRL was measured daily until embryonic cardiac activity appeared, then at intervals of 2 or 3 days, depending on the availability of the women and the travelling distances involved, until day 42.

All the women were scanned between 10·00 and 12·00 hours using Diasonics DRF 400 and Toshiba SAL 77B transvaginal probes. The former was equipped with a 5·0 and a 7·5 MHz mechanical sector scan transducer and the latter with a 5·0 MHz electronic sector scan transducer. Scans were recorded by RS and CAMJ.

A reference chart (mean ± 1SD) was constructed from all the longitudinal CRL data. In 11 normal subjects with naturally conceived pregnancies (15 embryos) four consecutive blind determinations of the CRL were obtained to establish the intra-observer variability of these measurements. Inter-observer variation was tested in 12 other normal subjects with single,

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naturally conceived pregnancies. Intra- and inter-observer variability was determined by the coefficient of variation; the inter-observer variation was also submitted to the Wilcoxon two-tailed rank test to evaluate systematic differences between the two observers.

Results

The intra- and inter-observer variability showed a coefficient of variation of 6·6% and 8·4% respectively. There was no statistically significant systematic difference between the observers ($P = 0{\cdot}38$).

In 8 of the 41 women we were unable to time the onset of embryonic cardiac activity and therefore we also missed the first CRL measurements, due to factors such as non-availability of the women when required. Incomplete data from these eight women (five singleton and three twin pregnancies) together with the complete data from the other 33 women (21 singleton, nine twin and three triplet pregnancies) were available for further analysis. In total 293 CRL measurements were obtained from 59 embryos. The number of CRL measurements varied between four and eight per embryo (median six) and between 10 and 30 per day of gestation (median 17). On day 25 after follicle aspiration only two CRL measurements could be obtained (1·2 and 1·6 mm respectively); they were excluded from the reference chart. Figure 1 depicts the CRL reference chart derived from the remaining transvaginally recorded CRL measurements, compared with the reference chart by Robinson & Fleming (1975).

Discussion

Our transvaginal CRL measurements demonstrate an acceptable intra- and inter-observer variability. Particularly in the very early weeks of gestation there is a discrepancy between our data and those compiled by Robinson & Fleming (1975). We have referred, for comparison, to their original data instead of the chart constructed from linear regression analysis. Inclusion of part of the yolk sac may have been responsible for the larger CRL measurements at the earliest gestational age in the reference chart obtained previously by compound B-scan equipment. Degenhardt *et al.* (1988) have also reported smaller early CRL values using transvaginal sonography, but the number of CRL measurements per day of gestation was considerably smaller than in our study: 225 measurements in 209 subjects between 6 and 13 weeks of menstrual age. The smaller standard deviation displayed in our chart can be explained by (i) the high resolution capability of modern transvaginal transducers allowing more detailed identification of embryonic structures, (ii) the larger number of CRL measurements per pregnancy and (iii) knowledge of the exact duration of the pregnancy. The advantage of studying IVF pregnancies is that the precise time of ovulation (follicle aspiration) and embryo transfer are known. Whether the results can be extrapolated to naturally conceived pregnancies is uncertain. We included multiple pregnancies because the embryos behave like separate individuals with their own growth profile and developmental potential; in a number of cases we even observed a difference in the time of appearance of embryonic cardiac activity and in subsequent CRL values (Schats *et al.* 1988). It is of interest that transvaginal CRL measurements were obtained approximately 4 days earlier than reported previously (Robinson & Fleming 1975), which could allow earlier pregnancy dating in the event of an unreliable menstrual history. We conclude from the present study that transvaginal sonography allows more detailed

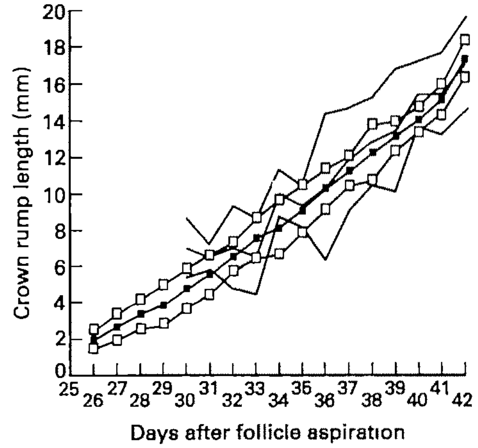

Fig. 1. Reference chart for embryonic crown rump length (CRL) in early pregnancy. Data derived from transvaginal ultrasound measurements (—■— mean, —□— ± 1SD) superimposed on the original data (— mean, — ± 1SD) collected by Robinson & Fleming (1975).

recognition of embryonic anatomy and, therefore, earlier and more accurate measurements of embryonic CRL. A larger transverse study, preferably in women with naturally conceived pregnancies, should be initiated to construct a new reference curve for this scanning technique.

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Immunohistological demonstration of intermediate trophoblast in the diagnosis of uterine versus ectopic pregnancy: a retrospective survey and results of a prospective trial

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Summary. Immunohistological demonstration of human placental lactogen (hPL) in non-villous, mononuclear intermediate trophoblastic cells may be of routine diagnostic value, when chorionic villi are absent in endometrial curettings from patients suspected of miscarriage of an intrauterine pregnancy. The histological presence and distribution of hPL was investigated in endometrial curettings from 90 patients studied retrospectively (47 had ectopic pregnancies, 14 miscarriages, and 29 legal abortions), and a consecutive, prospective series of 50 patients (40 had miscarriages and 10 had ectopic pregnancies) without chorionic villi in their endometrial curettings. Non-specific background staining was not a problem. The retrospective survey disclosed that hPL was a highly sensitive marker of intrauterine pregnancy (sensitivity = 0·98). In the prospective series, the predictive value of positive staining for hPL for intrauterine pregnancy was 1·00, and the sensitivity of hPL, as an indicator of uterine gestation, was 0·62. In absence of specific hPL-staining, the risk of ectopic pregnancy was about 50%. The immunohistochemical demonstration of hPL is a useful tool for identifying patients who are suspected of having had a miscarriage, but for whom evidence in the form of chorionic villi in endometrial curettings is lacking.

The absence of chorionic villi in endometrial curettings from patients suspected of having miscarried an intrauterine pregnancy may give rise to diagnostic problems related to uncertainties about the presence of an ectopic pregnancy. In these cases either direct, surgical intervention or

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extensive follow-up, including physical examination and monitoring of hormones, are necessary. Both place demands on clinical resources and result in considerable psychological distress for the patient. Recent advances in immunohistochemistry may provide the pathologist with a specific technique for the diagnosis of uterine gestation in such cases.

Non-villous mononuclear trophoblastic cells are morphologically difficult to distinguish from endometrial stromal cells showing decidual reaction. However, the former cells can be identified on the basis of their rich content of human placental lactogen (hPL) (Gosseye & Fox 1984; Kurman *et al.* 1984a). The cells represent a transitional form of trophoblast, which has cytological, ultrastructural, immunohistochemical and functional features that are distinct from those of cyto- and syncytiotrophoblast. They have been termed 'intermediate trophoblast' (Kurman *et al.* 1984a,b). The possibility of immunohistological demonstration of intermediate trophoblastic cells as an aid to the diagnosis of intrauterine gestation in the absence of chorionic villi has already been addressed in retrospective studies (Heyderman *et al.* 1981; Angel *et al.* 1985; O'Connor & Kurman 1988). In the study presented here the presence and distribution of hPL in the non-villous intermediate trophoblast of uterine pregnancies have been studied. In addition, a consecutive, prospective series of patients was studied to assess the 'true' diagnostic value of the method for distinguishing uterine and ectopic pregnancies in routine, clinical conditions.

Patients and methods

Patients

Group A, Negative and positive control. Five non-pregnant patients, who had endometrial curettage for menstrual irregularities, and three patients clinically suspected of miscarriage, but without chorionic villi in their endometrial curettings, were retrospectively selected from the files of the University Institute of Pathology, Aarhus Kommunehospital. Histological specimens from these two groups of patients were used in a pilot study for testing the method and for adjusting the immunohistochemical technique. Histological sections from these patients served as negative and positive controls, respectively.

Group B, Ectopic pregnancies. Forty-seven patients with ectopic pregnancies between 5 and 12 weeks gestation (mainly located in the fallopian tubes) who, in addition to the surgical removal of the ectopic pregnancy, also had an endometrial curettage. The surgical approach was approved by the local ethics committee.

Group C, Miscarriages. Fourteen patients, who miscarried between 5 and 12 weeks gestation. All had uterine curettage and only the specimens removed surgically were investigated, because tissue passed spontaneously was not often available.

Group D, Legal abortions. Twenty-nine patients, who had legal abortions between 7 and 15 weeks gestation (only one patient was in the second trimester).

Group E, Prospective trial. A consecutive series of 50 patients (mean age 28 years, range 16–42 years), clinically suspected of miscarriage at 5–13 weeks gestation but without chorionic villi in the endometrial curettings, was collected over a period of 6 months. All material from each patient was immunohistologically stained, and examined by one of a group of seven pathologists, who were blind to the category of patient. The time required for immunohistological staining was recorded. The immuno-diagnoses were withheld for 6 months and were not used in the clinical management of the 50 patients.

Histological specimens

The specimens obtained from within the uterus were processed routinely and embedded in paraffin. Histological sections of 4 μm thickness were stained with haematoxylin and eosin for routine morphological diagnosis. All tissue from patients in groups B, C, and E were investigated, whereas only one slide that included extra-villous tissue was selected from each patient of group D.

Immunohistochemistry

After deparaffinization and rehydration, the histological sections were stained for hPL-antigen with a slightly modified version of the three-stage peroxidase-antiperoxidase technique described by Taylor (1978). The primary antibody was rabbit polyclonal anti-hPL, at a titre of 1:1000, incubated overnight. The secondary antibody was swine anti-rabbit immunoglobulin, and the third stage was horseradish peroxidase rabbit anti-horseradish peroxidase (PAP) complexes (all antibodies obtained from DAKO, Copenhagen). Endogeneous peroxidase was inactivated by incubation with methanol (Merck no. 6009) containing 2% (vol/vol) of a 35% H_2O_2-solution. A primary incubation was carried out with 0.1% trypsin (Sigma no. T-8128). Fetal calf serum (MEDA-Gibco no. 011-6290H) was added to all buffer solutions in 1% concentration to reduce non-specific staining, and 3.3-diaminobenzidine tetrahydrochloride (DAB) was used as chromogen. The immunohistological slides were counterstained by Mayer's haematoxylin and cover-slipped using Kaiser's gelatine (Merck no. 9242). With each batch of slides, known positive and negative control slides were included (group A) together with a positive control, in which the primary antibody was omitted.

Clinical records

Information on the clinical diagnosis and outcome was kept separately.

Immunohistological assessment

All immunohistochemically stained histological slides, except for specimens from patients of group E, were examined independently by two observers. Scoring involved the: (a) presence of chorionic villi, (b) staining and location of hPL, and (c) assessment of non-specific background staining. Positive immunohistochemical demonstration of mononuclear, intermediate trophoblastic cells demanded a specific, cytoplasmic staining for hPL (specific hPL).

Statistics

A 2×2 table was constructed to assess the predictive value of positive and negative immunostaining in relation to the miscarriage of an intrauterine pregnancy and an ectopic pregnancy. The specificity, sensitivity and the predictive powers of a positive and negative test were calculated by standard methods.

Results

Retrospective study

Controls. Endometrial specimens from patients in group A with menstrual irregularities were not stained by antibodies against hPL. Non-specific background staining was visible in most cases, and a slight cross-reaction was demonstrated in endocervical columnar cells and isolated squamous epithelial cells from the ectocervix. There were, however, no difficulties in the immunohistological identification of the slides as not containing hPL-positive intermediate trophoblast. Endometrial stromal cells were invariably immunonegative.

In contrast, the three endometrial specimens without villi, from patients suspected of miscarriage, showed marked immunoreactivity. Sparse fragments of syncytiotrophoblast reacted slightly with antibodies to the hPL antigen. Large numbers of mononuclear intermediate trophoblastic cells in the endometrial stroma showed a clear hPL-specific reaction (Fig. 1). These cells had a tendency to align around endometrial vessels (Fig. 2), but the staining pattern was uniform throughout the extra-villous tissue. The surrounding decidualized stroma cells were clearly negative for specific hPL. Focal secretions within endometrial glands stained slightly, as did the non-specific background staining mentioned above. Higher dilutions of antibodies reduced both the non-specific background staining and the specific trophoblastic immunostaining. No differences in scoring were encountered between the observers.

Ectopic pregnancies. Endometrial curettage from one patient contained only endocervical fragments. The remaining 46 patients with ectopic pregnancies contained sufficient endometrial tissue for immunohistochemical investigation. In all cases the endometrium was negative for specific hPL. Non-specific, slight staining was observed in clumps of squamous epithelium, fragments of endocervical epithelium, and in the secretions in the glandular lumina of the endometrium. The glandular epithelium, even when there was a pronounced Arias Stella phenomenon, was almost free of non-specific staining. Endometrial specimens from two patients in this group had focal, interstitial precipitates of chromogen, but in none of these cases were there discrepancies between the observers with regard to the classification of the immuno-reaction as non-specific for hPL.

Miscarriages. In 13 specimens, chorionic villi and extra-villous tissue were recognized morphologically. hPL was detected in both the syncytio- and cytotrophoblastic cell layers of villi, though only weakly in the latter. In the villus cores, a few Hofbauer cells stained slightly. In

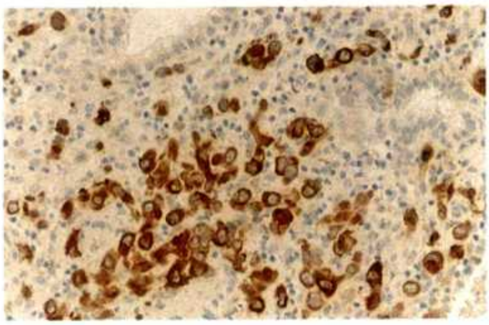

Fig. 1. Section from the implantation site of a pregnancy that miscarried at 8 weeks gestation stained by antibodies to human placental lactogen (hPL). An intense cytoplasmic reaction for hPL is seen in mononuclear, intermediate trophoblastic cells in the endometrial stroma surrounding endometrial glands (magnification 132×; Mayer's haematoxylin counterstain).

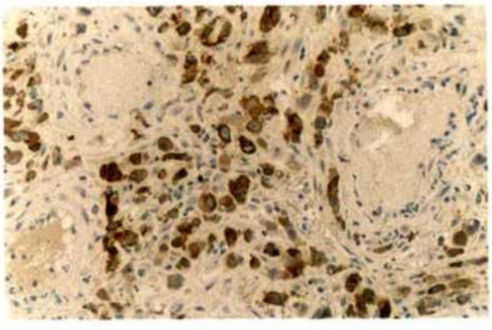

Fig. 2. Intermediate trophoblastic cells in the endometrial stroma surrounding vessels of the implantation site show an intense cytoplasmic reaction for human placental lactogen (hPL) antigen (same case as in Fig. 1; magnification 132×; Mayer's haematoxylin counterstain).

the extra-villous tissue, the specific staining pattern seen in the positive controls in group A was easily recognized. Non-specific background staining was weak and total agreement between the observers was achieved. In one patient, no villi were found and no recognizable extra-villous, specific hPL-staining was demonstrable. The endometrium showed a marked Arias Stella-reaction with large areas of necrosis. The clinical history suggested the possibility of a complete miscarriage 1 to 2 days before uterine curettage. Laparoscopy showed no signs of ectopic pregnancy.

Legal abortions. Uterine aspirates from three patients contained only villi and were excluded. Of the remaining 26 specimens, 25 included fragments of extra-villous tissue with a specific immuno-reaction similar to the described pattern for group C. One specimen from this group of patients was without villi, but a strong, specific reaction for hPL was seen. Background staining was weak resulting in total diagnostic agreement.

Diagnostic accuracy in retrospective study. A summary of the results from groups B, C and D is shown in Table 1. The sensitivity of the method using hPL as an indicator of uterine pregnancy was 0·98 (95% CI 0·87–1·00) and the specificity was 1·00 (0·92–1·00). The predictive value of a positive test suggesting uterine miscarriage was 1·00 (0·91–1·00), whereas the predictive value of a negative test in the diagnosis of ectopic pregnancy was 0·98 (0·89–1·00).

Prospective study. Six patients were excluded from further analysis, because ultrasound examination showed intrauterine pregnancies (gestation sac with a fetus, some with heart movements). Among these six patients, five had specific hPL-reactions, whereas in one there was absence of specific hPL-staining in the endometrial curettage. The remaining 44 patients were, at the time of endometrial curettage, suspected of miscarriage. Among these patients, ten were diagnosed later to have had ectopic pregnancies. The results of the immunohistological investigation are shown in Table 2. The sensitivity of hPL as a marker of uterine pregnancy was 0·62 (95% CI 0·44–0·78). The specificity for uterine pregnancy was 1·00 (0·69–1·00). The predictive value of a positive test was 1·00 (0·83–1·00) for uterine pregnancy, and 0·44 (0·27–0·57) for ectopic gestation with a negative test in the 44 patients investigated. In five the pathologists were unable to score the hPL-immunostaining as positive or negative. These patients are listed as negative in Table 2, and none had an ectopic pregnancy. The time needed for an immunohistological diagnosis was on average 58 h (range 24–121 h), including periods during which the sole laboratory technician engaged by the project was ill or on vacation.

Discussion

In 31% of patients suspected of uterine miscarriage chorionic villi may be absent in the endometrial curettings (Sikjær 1979). The clinical difficulties in assessing these patients are so great that every improvement on the diagnostic scale will be of benefit.

Table 1. Distribution of human placental lactogen (hPL)-immunostaining pattern in endometrial curettings according to the clinical diagnoses of 86 patients investigated retrospectively

	Clinical diagnosis			
Intermediate trophoblast	Miscarriages	Induced abortions	Ectopic pregnancies	Total
hPL-positive	13	26	0	39
hPL-negative	1	0	46	47
Total	14	26	46	86

Macroscopically, fresh endometrial specimens immersed in isotonic saline may reveal the typical 'hardwood-like' structure of chorionic villi, but this method is not diagnostically reliable. Deeper section levels of the paraffin-embedded tissue blocks, initially lacking villi, may disclose villi and confirm the diagnosis of intrauterine pregnancy. However, when chorionic villi are not seen, the routine histological diagnosis must be based on other morphological signs of intrauterine gestation. The giant cells of 'syncytial endometritis' favour a diagnosis of placental site, but they may be very difficult to identify. Other suggestive, but non-diagnostic, histological signs of intrauterine pregnancy are hyalinized vessels and fibrinoid (O'Connor & Kurman 1988). Morphological interpretation of the non-villous trophoblast in human pregnancy is demanding. However, it has been possible to discern mononuclear, invasive trophoblastic cells of interstitial localization in the endometrial stroma (especially around the uterine spiral vessels), and endovascular trophoblastic cells (Pijnenborg *et al.* 1980). Morphological evidence points to a migration of mononuclear trophoblastic cells from the anchoring villi, followed by invasion of the decidua and the myometrium of the uterine wall (Pijnenborg *et al.* 1981). The population of mononuclear trophoblastic cells, diffusely infiltrating between native endometrial stromal cells, has been termed intermediate trophoblast. These cells are either rounded or polyhedral. The latter types may be very difficult to distinguish from decidual cells. They are about twice the size of villous cytotrophoblastic cells, mostly due to an increased amount of cytoplasm. The nuclei vary in shape from round and lobated to ovoid without any distinctive chromatin pattern and contain a few prominent nucleoli (Kurman *et al.* 1984a). From the morphological point of view, the intermediate trophoblastic cells have been shown to be the single most useful feature when confirming the presence of intrauterine gestation in the absence of chorionic villi or a fetus (O'Connor & Kurman 1988).

Table 2. Distribution of human placental lactogen (hPL)-immunostaining pattern in endometrial curettings according to the clinical diagnoses of 44 patients investigated prospectively who did not have chorionic villi in their endometrial specimens

	Clinical diagnosis		
Intermediate trophoblast	Miscarriages	Ectopic pregnancies	Total
hPL-positive	21	0	21
hPL-negative	13*	10	23
Total	34	10	44

*Includes five patients where the pathologists were unable to score the hPL-immunostaining as positive or negative.

The hPL-antigen is an accurate marker for the intermediate trophoblast (Gosseye & Fox 1984; Kurman *et al.* 1984a,b). Human chorionic gonadotrophin (hCG) has been demonstrated immunohistologically in intermediate trophoblastic cells, but the staining pattern seemed focal and rather weak, compared to that of antibodies to hPL (Kurman *et al.* 1984a; Angel *et al.* 1985). This finding was confirmed in our pilot study, carried out during the planning of the present investigation. We therefore decided to focus exclusively on the clinical value of immunohistological demonstration of hPL. Other antibodies have been produced to localize trophoblastic cells in routine fixed specimens. Murine monoclonal antibodies against trophoblastic antigens have been investigated, but also suffer from cross-reactivity with the columnar epithelium or endometrial glands throughout the first trimester (Bulmer *et al.* 1984). Monoclonal antibodies against cytokeratins have been shown to stain both villous and non-villous trophoblasts at the implantation site, but likewise stain endocervical and endometrial gland columnar epithelium (Sasagawa *et al.* 1986). Although glandular epithelial cells are mostly morphologically discernible, cross reactivity and background staining are crucial factors for the reliable assessment of endometrial curettings from patients who might have an ectopic pregnancy. In the present study false positive test results were not encountered.

The infiltrating, mononuclear, intermediate trophoblastic cells were stained intensely and specifically by antibodies against hPL in all but one of specimens examined retrospectively in which there was intrauterine gestation and remnants of the non-villous placental site. The identification of intermediate trophoblastic cells was highly specific, and the diagnostic accuracy of intrauterine gestation 100%. Similar results from retrospective studies have been reported (Angel *et al.* 1985; O'Connor & Kurman 1988).

The results from the prospective part of the present investigation show the true value of the immunohistological approach to patients, who are suspected of the miscarriage of an intrauterine pregnancy but lack villi in their endometrial curettings. Used in a routine setting, the sensitivity decreased, but no false positive immunohistological results occurred. The results are promising, because the immunohistological test for presence of hPL allows a more selective approach to these patients. About 50% of the patients suspected of uterine miscarriage, but lacking chorionic villi in their endometrial specimens, were diagnosed to have had intrauterine pregnancies on the basis of the hPL-test. Accordingly, when used under routine clinical conditions, ectopic pregnancy can be excluded in these patients. In contrast, the other half of the prospective series with a negative hPL-test represents a high-risk group of patients, of whom about 50% had an ectopic pregnancy. This indicates that the hPL-test may allow exclusion of patients with low or no risk from clinical follow-up. The available resources may instead be utilized more efficiently on the reduced number of patients in the high-risk group. Fortunately, no risk is involved with false negative hPL-immunostaining results, because these patients will be managed as possible ectopic pregnancies. The time required for an immunohistological diagnosis is a major difficulty in the routine use of this method. However, only one technician was engaged in tissue processing and immunostaining in this study. If the immunodiagnosis can be made within 24 h, a considerable number of patients will not need close clinical follow-up to exclude ectopic gestation. The immunohistological approach is, unfortunately, invalid when there are combined ectopic and uterine gestation. The incidence of combined pregnancies has in a recent review been estimated to about 0·026% (Bello *et al.* 1986). Awareness of this possibility is the most important aspect for the correct management of such patients.

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The role of vaginal scan in measurement of endometrial thickness in postmenopausal women

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Summary. Transvaginal ultrasound scanning was performed on 111 postmenopausal women. Of these women, 103 had postmenopausal bleeding, and eight were undergoing hysterectomy. Of the 103 women with bleeding, 93 had dilatation and curettage (D&C) and 10 patients were treated conservatively with a repeat scan in six months. A correlation of ultrasound findings and endometrial histopathology was possible in 94 patients. In 59 of these (63%) the endometrium was atrophic and the ultrasound endometrial thickness was 5 mm or less. In 29 (31%) patients the endometrial histology was abnormal and ultrasound endometrial thickness was greater than 5 mm. In six patients the endometrium was atrophic, but the ultrasonic endometrial thickness was apparently greater than 5 mm due to intracavity fluid. We suggest that an endometrial thickness of 5 mm is an appropriate cut-off level for conservative management of patients with postmenopausal bleeding, or in screening for endometrial carcinoma.

Postmenopausal bleeding is widely recognized as an early presenting feature of endometrial carcinoma (Ross 1988). The overall 5-year survival of endometrial carcinoma is 65% and during the last 20 years there has been no improvement in this figure (Annual Report on the Results of Treatment in Gynaecological Cancer 1989).

The sonographic findings in endometrial carcinoma include intrauterine fluid collections, thickened and/or highly reflective endometrium, and irregular endometrium with mixed reflectivity. A normal ultrasound appearance of the endometrium in postmenopausal women has been found to exclude endometrial pathology (Fleischer *et al.* 1987; Nasri *et al.* 1989). These studies used transabdominal ultrasonography and the recent introduction of transvaginal ultrasound scanning has permitted the use of higher frequency ultrasound at greater proximity to the uterus and the endometrial-myometrial interface can be seen more clearly than with the full bladder transabdominal technique. A disadvantage of transvaginal ultrasound is the limited field of view, especially for patients with extensive adnexal lesions, but this is not relevant when the endometrium is the primary target (Mendelson *et al.* 1988).

The present study was designed to determine the value of transvaginal ultrasound scan in

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detecting endometrial pathology in postmenopausal women, with particular reference to screening for precancerous lesions, mainly endometrial hyperplasia and endometrial polyps.

Patients and methods

Transvaginal ultrasound scans were recorded in 111 postmenopausal women. Their mean age was 60 years (range 45–97); three women were taking hormone replacement therapy (HRT). Of these 111 women, 103 had postmenopausal bleeding the other eight had no bleeding and were having a hysterectomy for prolapse and/or CIN lesions. Of the 103 women with bleeding, 93 had a dilatation and curettage (D&C) and 10 were treated conservatively with a repeat scan six months later.

Postmenopausal bleeding was defined as vaginal bleeding at least six months after cessation of the menses. Ultrasound examination used an ALOKA SSD-620 machine with a 5 MHz, electronic convex sector transducer. This has a scanning angle of 60° and the point of maximum focus is 5 cm (range 2·5–7 cm). The length of the probe is 17 cm and the length of the handle is 12 cm. The widest diameter of the probe footprint is 2·5 cm. The probe was placed inside a condom containing coupling gel. Additional gel was placed on the covered probe. Endometrial thickness was measured from the highly reflective interface of the junction of the endometrium and myometrium. This measurement represents two layers of endometrium (Fleischer *et al.* 1986a). The surrounding low amplitude echo layer was not included in the measurement, as this represents the inner layers of compact and vascular myometrium (Fleischer *et al.* 1986b). This layer is symmetrical and intact in all normal postmenopausal uteri and also in all those with endometrial polyps, and simple and atypical hyperplasia. It is absent or irregular in uteri with invasive endometrial carcinoma (Nasri *et al.* 1989; Fleischer *et al.* 1987). Using the calipers of the ultrasound machine, the endometrial line was measured at its maximum thickness in both horizontal and vertical planes regardless of the position of the uterus (Fig. 1) The average thickness was taken as an accurate representation. To localize the uterus in the presence of uterovaginal descent, the probe should be inserted mid-way in the vagina; deeper insertion may by-pass the prolapsed uterus. Each examination took between 5 and 10 min. This form of scanning was well tolerated by all patients, avoiding the discomfort associated with the transabdominal full bladder procedure.

Results

In the eight women with no postmenopausal

Table 1. Ultrasound and histological findings in 93 women with postmenopausal bleeding

Ultrasound findings				
Diagnosis	*n*	Endometrial thickness* (mm)	Histological findings of D&C	*n*
PM uterus	51	3·1 (1–5)	No material	37
			Inactive endometrium	14
PM uterus+ intracavity fluid	6	6.8 (6–8)	No material	2
			Mucus	4
PM uterus+ endometrial polyp	6	14 6 (6–26)	Benign endometrial polyps	6
PM uterus+ endocervical polyp	4	11.7 (6–18)	Benign cervical polyps	4
Diffuse hyperplasia	10	14 4 (9–25)	Simple hyperplasia	7
			Atypical hyperplasia	3
Carcinoma	6	22 2 (8–38)	Endometrial carcinoma	6
Intracavity fluid	3	21.3 (11–42)	Pyometra	3
Miscellaneous	3	42 mm	Predecidual changes	1
		7 mm	Proliferative endometrium	1
		12 mm	Menstrual endometrium	1
Fibroid distort cavity	4		See text	

*Values are given as means (range) where appropriate
PM = Postmenopausal.
D&C = Dilatation and curettage.

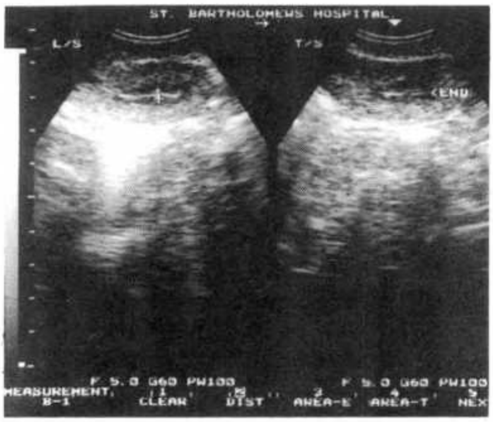

Fig. 1. TVS showing a normal postmenopausal uterus in both horizontal and vertical planes (T/S and L/S) with a central echo endometrium (END), and a subendometrial halo.

bleeding the mean endometrial thickness was 2·6 mm (range 1–4 mm) and histology confirmed inactive endometrium. In the 10 women treated conservatively the mean endometrial thickness was 2·9 mm (range 2–4 mm). Repeat scanning six months later showed no change in endometrial thickness. There was no recurrence of symptoms. Table 1 shows the ultrasound and histological findings in the 93 women with postmenopausal bleeding who had a dilatation and curettage. In 51 patients ultrasound showed a normal postmenopausal uterus. The uterine cavity appeared as a linear central echo oriented in the cranio-caudal axis with a subendometrial halo (Fig. 1). Inactive normal endometrium was found in 14 women and there was no tissue on curettage in 37 women. In one of these women the uterus was perforated. Another had both vaginal bleeding and haematuria. Ultrasound scan showed an endometrial thickness of 2 mm and histology confirmed an inactive endometrium. Cystoscopy and bladder biopsy demonstrated a papillary G1 transitional cell carcinoma of the bladder wall. Ectocervical polyps were removed in three patients. In six patients there were small sonolucent areas in the uterine cavity that separated the most superficial layers of the endometrium. Both the anterior and posterior endometrial linings were very thin (Fig. 2). In two of these women there were no curettings, and in four only mucus was obtained.

Uterine polyps were diagnosed in ten women, four endocervical and six endometrial. In a longitudinal plane the endocervical polyps appeared as localized thickenings of the endometrium close to the internal os, but in a transverse plane the cervical canal was dilated and contained a mixed echogenic structure (Fig. 3). Endometrial polyps were diagnosed ultrasonically by the presence of a well-defined local thickening of the endometrium with increased reflectivity, surrounded by a symmetrical area of low amplitude echoes; the cranial part of the uterine axis was thinner than the caudial part (Fig. 4). Endocervical polyps were diagnosed accurately by ultrasound in two women, but in the other two an erroneous diagnosis of endometrial polyps was made. Endometrial polyps were diagnosed by ultrasound in four of six women, but in the remaining two only a thickened endometrium of apparently normal texture was seen.

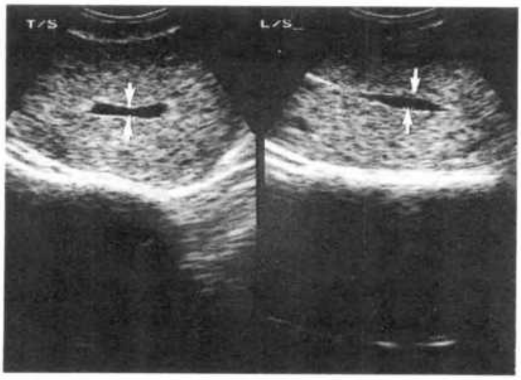

Fig. 2. TVS showing a normal postmenopausal uterus in both horizontal and vertical planes (T/S and L/S) with thin endometrial linings (arrows) and small sonolucent area in the uterine cavity.

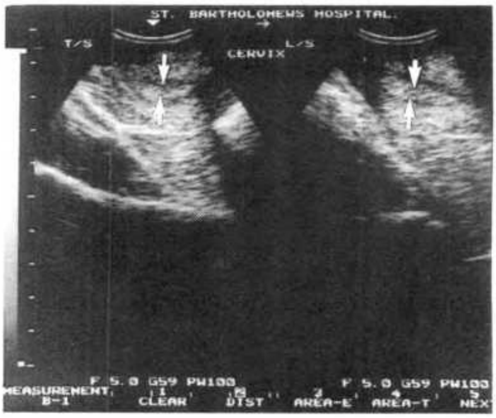

Fig. 3. TVS at the region of the cervix in both horizontal and vertical planes (T/S and L/S) showing an endocervical polyp (see arrows).

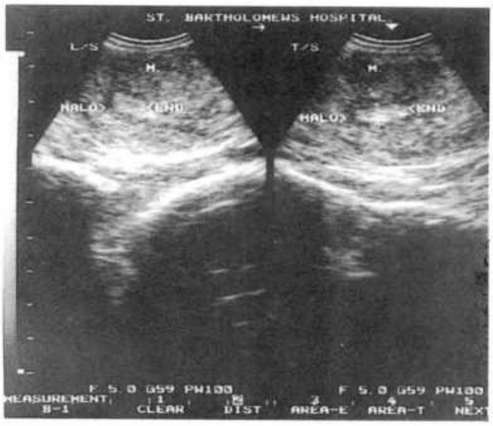

Fig. 4. TVS of the uterus in both horizontal and vertical planes (T/S and L/S) showing an endometrial polyp (END) surrounded by a symmetrical area of low amplitude echo (HALO). 'M' is myometrium.

In 10 patients ultrasound showed a well defined, thick and highly reflective layer occupying the whole of the endometrial cavity and surrounded by a symmetrical poorly reflective zone (Fig. 5).

This picture was highly suggestive of endometrial hyperplasia. Histology revealed simple diffuse hyperplasia (cystic glandular hyperplasia) in seven and atypical hyperplasia in three women. In six women ultrasound correctly predicted carcinoma of the endometrium. The lesion appeared as an irregular, thickened, highly reflective area of endometrial lining with loss of the surrounding symmetrical area of low amplitude echoes. In one case the lesion was a polypoid highly reflective mass and the remainder of the uterine cavity showed poor reflectivity (Fig. 6). Histology confirmed invasive endometrial adenocarcinoma in all six women.

In three patients ultrasound showed an echo-free and irregularly widened uterine cavity (Fig. 7); curettage showed a pyometra. An abnormal cervix was shown in two patients, and biopsies showed invasive squamous cell carcinoma. The third patient had worn a ring pessary for many years.

Uterine fibroids were present in 16 women, but in only four the endometrial line was not seen due to the presence of multiple fibroids distorting the endometrial cavity. Curettage showed inactive postmenopausal endometrium.

In one patient ultrasound showed a bulky uterus with an endometrial thickness of 42 mm. The endometrium showed multiple sonolucent structures with areas of high reflectivity, similar to a hydatidiform mole (Fig. 8). Histology showed widespread 'predecidual' changes. These changes were mostly due to the hormonal treatment of her breast cancer (tamoxifen followed by Provera). In another patient ultrasound showed a 7 mm endometrium and a simple ovarian cyst (14 × 8 × 7 mm). Histology showed proliferative endometrium. A third patient had a 12 mm endometrium; histology showed menstrual type endometrium. Figure 9 illustrates the relation between the average ultrasound endometrial thickness and the histological findings in 94 postmenopausal women. In 59 patients (51 with PMB and eight without) with normal ultrasound findings and an inactive postmenopausal endometrium the endometrial thickness ranged between 1 and 5 mm. In six patients the endometrium was atrophic, but the ultrasonic endometrial thickness was apparently greater than 5 mm due to intracavity fluid. In 29 women with

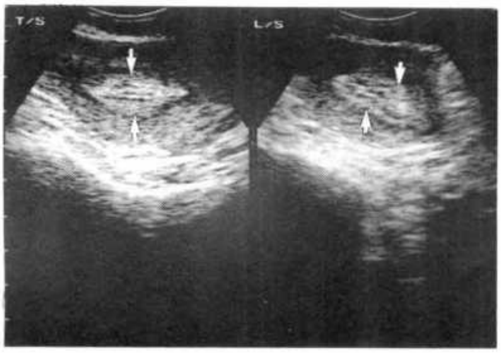

Fig. 5. TVS of the uterus in both horizontal and vertical planes (T/S and L/S) showing endometrial hyperplasia (see arrows) with a subendometrial halo.

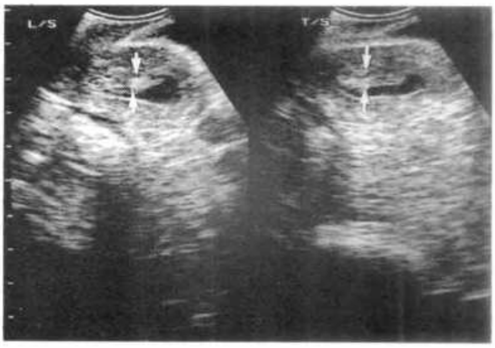

Fig. 6. TVS in the uterus in both horizontal and vertical planes (T/S and L/S) showing a polypoid endometrial carcinoma (arrows) and entrapped fluid.

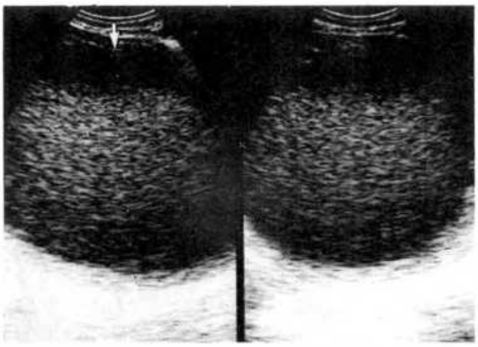

Fig. 7. TVS in the uterus in both horizontal and vertical planes showing a huge pyometra (arrows).

abnormal scan findings the endometrial thickness was more than 5 mm. Thus if the endometrial thickness is 5 mm or less throughout the uterine cavity in a postmenopausal woman, the endometrium will be atrophic and probably inactive. If there is focal or generalized endometrial thickness of more than 5 mm then pathology should be expected, although in some cases this will be intracavity fluid only.

Discussion

Transabdominal ultrasound permits study of the endometrium in both longitudinal and transverse sections of the uterus (Nasri *et al.* 1989). However, with transvaginal ultrasound the position of the uterus may be difficult to identify. Because of this, together with uterovaginal descent, the postmenopausal endometrium may not appear as a continuous line in every patient.

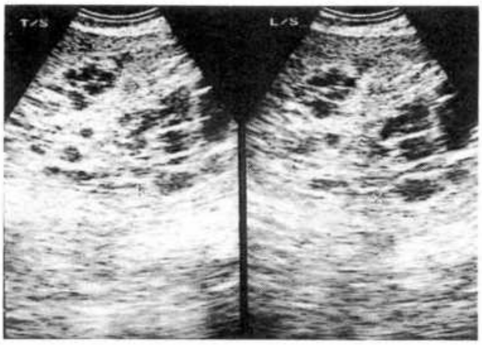

Fig. 8. TVS in the uterus in both horizontal and vertical planes showing multiple sonolucent structures with areas of high reflectivity, 'predecidual changes'.

Because the bladder is empty, transvaginal ultrasound missed a diagnosis of bladder carcinoma in a patient with an atrophic endometrium. By contrast, in a previous study using abdominal ultrasound, one patient had a normal postmenopausal uterus, but a thickened bladder wall; subsequent cystoscopy and biopsy showed granulation tissue and an inflammatory exudate (Nasri *et al.* 1989).

The proximity of the transvaginal probe to the endometrium and the absence of the full bladder compressing the endometrium revealed a group of patients with an atrophic postmenopausal uterus but ultrasonic endometrial thickness of more than 5 mm. In this group there was separation of the superficial layers of the endometrium by intracavity fluid. The actual thickness of each of the anterior and posterior endometrial walls was 1–2 mm. This phenomenon must be identified and excluded if the cut-off level of 5 mm is to be used.

Two patients had endometrial polyps which were not diagnosed by scan, and two endocervical polyps were interpreted as endometrial polyps. Although endocervical polyps are easy to diagnose clinically, gradual introduction of the probe to the mid-vagina in the horizontal plane will show the cervix and identify any dilatation of the cervical canal associated with endocervical pathology. Rotation of the probe through 90° will then bring the cervix into a longitudinal view and thus confirm any endocervical pathology. In all ultrasound-predicted endometrial polyps, tissue diagnosis is advisable as Pettersson *et al.* (1985) have shown that endometrial polyps are associated with a threefold

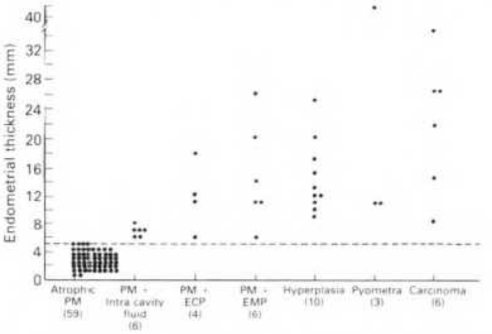

Fig. 9. Relations between endometrial thickness measured by ultrasound and histological findings in 94 postmenopausal women. The dashed line shows the cut-off level of 5 mm for abnormal findings. PM = postmenopausal uterus; ECP = endocervical polyp; EMP = endometrial polyp.

increase in the risk of endometrial carcinoma. In the present study three women were taking HRT. One woman who had received unopposed oestrogen (premarin) for 20 years had an endometrial thickness of 26 mm; histology showed moderately differentiated adenocarcinoma spreading into the outer one third of the myometrium. A second woman on combined HRT therapy had an endometrial thickness of 12 mm; histology confirmed atypical cystic glandular hyperplasia. Another woman on combined HRT for 30 years had an endometrial thickness of 12 mm; histology showed normal menstrual type endometrium. This indicates that the cut-off level of 5 mm is not appropriate in women on HRT and tissue diagnosis is essential unless repeated scans can be made on a regular basis. Further study in this group of patients is needed before transvaginal ultrasound scan can be used for screening. Conservative management of a small group of 10 women, not taking HRT, gave promising results and suggests that this approach may be acceptable as the sole diagnostic procedure in selected patients with postmenopausal bleeding.

We recommend the routine use of transvaginal ultrasound for women with postmenopausal bleeding. It is a simple, non-invasive technique, and was found to be highly acceptable by patients. In cases in which the endometrium is ultrasonically normal the woman will be spared an unnecessary operation, an important matter in this age group. Based on this study using transvaginal ultrasound scan and on a previous one using transabdominal scanning on 179 patients, a cut-off level of 5 mm for endometrial thickness may be appropriate for a screening programme for endometrial carcinoma

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The use of Histoacryl for episiotomy repair

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Summary. Histoacryl-tissue adhesive (B. Braun Melsungen AG W. Germany) was used in place of skin sutures (2/0 chromic catgut, Ethicon Ltd, Edinburgh, Scotland) for episiotomy repair in a group of 20 women. This group was compared with two groups of women undergoing first and repeat episiotomy. Variables analysed included pain in the episiotomy site, pain while walking, sitting, sleeping, lying down, breast-feeding, micturating and defaecating. The Histoacryl group was superior with regard to all the variables. This simple, new method can reduce pain and inconvenience for patients, especially following the first delivery.

Thacker & Banta (1983) stated that pain following episiotomy appears to be almost universal, especially during walking and sitting. There is an extensive literature on the testing of therapies and different techniques to prevent pain. Therapies that have been used include enzymes, systemic pain medications, anti-inflammatory agents, local treatments such as local anaesthetics, gels and ointments, alternative methods of repair and alternative suturing materials (Grant 1989; Mahomed *et al.* 1989; Isager-Sally *et al.* 1986).

The purpose of this study was to determine whether Histoacryl-tissue adhesive (monomeric n-butyl-2-cyanoacryl, B. Braun), applied to the skin in place of stitches, can reduce the pain and discomfort originating at the mediolateral episiotomy site during the course of everyday activities.

Subjects and methods

There are about 300 deliveries per month at the Hadassah University hospital, Jerusalem. The incidence of first and repeat episiotomy is 17% and 10%, respectively. All episiotomies are mediolateral, and the size is usually no more than 6 cm. Usually, repairs are performed by the junior physician in the delivery room. In this study, only two of our staff physicians repaired the episiotomies using Histoacryl, or the traditional method.

Sixty women, divided into three equal groups, participated in the study. Group 1 comprised patients undergoing first episiotomy repaired by continuous 00-chromic catgut in the vagina, continuous stitches of the same material in the muscle, fascial layer and the skin. The stitches were not removed. Group 2 comprised patients undergoing repeat episiotomy, utilizing the above technique and group 3 comprised patients undergoing a first episiotomy utilizing the same technique as group 1, but using Histoacryl instead of stitches for the skin. A thin layer of tissue adhesive was applied to the dry and exactly apposed skin.

Groups 1 and 3 (first episiotomy repair) were selected randomly, by registration number, group 1 odd and group 3 even numbers. An explanation of the new method was given to the patients in group 3, all of whom agreed verbally to the repair using Histoacryl.

The degree of pain or discomfort was scored by a nurse, on the second postpartum day according to verbal responses on an ordinal scale ranging from 1 to 5 (one was the minimum and five the maximum). The nurse knew only that

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the patients had undergone episiotomy but knew nothing about the method of repair or whether it was first or repeat episiotomy, or whether the patient was included in the study group. The degree of reported pain at the episiotomy site, as well as pain and discomfort while walking, sitting, lying down, breast-feeding, sleeping and during micturition and defaecation were determined. Patients were also asked whether they needed analgesics or equipment designed to make sitting more comfortable.

Statistical analysis was performed using the Mann-Whitney *U*-test from the 'Crunch' statistical package version 3.

Results

Statistically significant differences between groups 1 and 2 (first episiotomy and repeat episiotomy) were found in three variables: pain at the episiotomy site (mean score 3·3, *vs* 2·6, $U = 107$, $P < 0{\cdot}01$), pain felt while walking (mean score 2·6 *vs* 1·9 $U = 103$, $P < 0{\cdot}008$) and sitting (mean score 3·6 *vs* 2·7, $U = 110$, $P < 0{\cdot}014$).

There were significant differences between the first episiotomy group (group 1) and the Histoacryl group (group 3) in five variables, pain at the episiotomy site (3·3 *vs* 1·95, $U = 56$, $P < 0{\cdot}001$), pain while sitting (3·6 *vs* 1·75, $U = 30{\cdot}5$, $P < 0{\cdot}0001$), lying down (2·35 *vs* 1·0, $U = 63$, $P < 0{\cdot}001$), walking (2·6 *vs* 1·6, $U = 30{\cdot}5$, $P < 0{\cdot}001$) and micturition (1·7, *vs* 1·0, $U = 120$, $P < 0{\cdot}03$).

The repeat episiotomy group (group 2) and the Histoacryl group (group 3) differed with regard to pain at the episiotomy site (2·55 *vs* 1·95, $U = 113$, $P < 0{\cdot}02$) and pain felt while sitting (2·7 *vs* 1·75, $U = 85{\cdot}5$, $P < 0{\cdot}001$).

No patients in the Histoacryl group needed analgesic drugs whereas eight patients (40%) in the first episiotomy group (group 1) and two patients (10%) in the repeat episiotomy group (group 2) used them.

No women in the Histoacryl group (group 3) needed sitting aids, while four patients (20%) in the first episiotomy group (group 1) and one patient in the repeat episiotomy group (group 2) needed them.

Discussion

It is not our intention to enter the debate as to the indications for performing episiotomies nor the benefits or harm, but rather to focus on the relief of pain caused by episiotomy.

The benefits and risks of episiotomy were summarized by Thacker & Banta (1983) in an excellent, comprehensive review. Since their review was published, several articles dealing with the problems of episiotomy-induced pain have appeared Isager-Sally *et al.* (1986) used three methods of repair. (1) Continuous no. 00-plain catgut in the vagina; no. 00-plain catgut interrupted stitches in the perineal muscles and fascia, and no. 00-nylon interrupted stitches in the skin. (2) The same technique as in (1), but with no. 0-polyglycolic acid (Dexon) in all layers. (3) The suture material as in (2), but used with a subcuticular technique. They found that the group using subcuticular stitches had the best results, regardless of the suture material. Grant (1989), in an overview of 14 controlled trials, found that derivatives of polyglycolic acid (Dexon & Vicryl) were the material of choice for deep and skin closure. Mahomed (1989) reported the same results, but found no difference between continuous subcuticular and interrupted transcutaneous sutures for repair of perineal skin.

Others have employed medication; Gleason *et al.* (1987) and Yonkeura *et al.* (1987) tried meclofenamate, a nonsteroidal anti-inflammatory drug, McMahon *et al.* (1987) and Ceccarelli *et al.* (1987) used flupirtine; Odigie (1988) used indomethacin suppositories.

Khan & Lilford (1987) recommend infiltration of the episiotomy site with saline before repair in women who are delivered under epidural analgesia, to reduce wound pain.

Harrison & Brennan (1987) used local anaesthetic in spray form for the relief of post-episiotomy pain. Greer & Cameron (1984) tried topical pramoxine and hydrocortisone foam for the same purpose.

An editorial in the *Lancet* (1989) refers to the misery suffered by women who have undergone episiotomy and mentions local and systemic treatments employed to relieve their pain. The article describes the use of ultrasound and/or pulsed electromagnetic energy as new methods for the local treatment of pain arising from the damaged perineum. Not only have the pain and misery induced by episiotomy continued, but they have probably increased as a result of the extended use of this procedure (Thorp & Bowers 1989).

In the present study, the best results were obtained with the group using Histoacryl, while the worst results were seen in the women having a first episiotomy repair in group 1. The use of Histoacryl, a simple technique, dramatically reduced the pain and discomfort encountered in everyday activities after episiotomy repair. The present results represent a short-term study. We intend to examine long-term sequelae in the future.

We recommend the use of Histoacryl as a simple method of reducing the pain caused by episiotomy repair.

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The tap test—a rapid bedside indicator of fetal lung maturity

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Summary. The reliability of two rapid bedside tests of fetal lung maturity was investigated in 80 amniotic fluid samples. The results of the 'tap' test and those of the shake test were compared with the results of laboratory measurements of phospholipid profiles for fetal lung maturity. The tap test was found to be more reliable with a positive predictive value of 91% and a negative predictive value of 63%, whereas the shake test had a positive predictive value of 79% and a negative predictive value of 31%. The tap test was also more reliable in identifying fetuses with borderline lecithin/sphingomyelin ratios in the range 3·2–3·7:1.

The ideal test for fetal lung maturity should be rapid, inexpensive, capable of being done at the patient's bedside, with a high predictive value for both mature and immature results.

Despite the numerous methods advocated for determining fetal lung maturity (Weiner & Weinstein 1987) it has been the practice in many obstetric units for the lecithin/sphingomyelin (L/S) ratio and amniotic fluid lecithin concentration to be the accepted means of surfactant assessment (Gluck *et al.* 1974; Donald *et al.* 1973; Gluck & Kulovich 1973; Gluck *et al.* 1971). However, these tests are costly and are not readily available outside normal working hours.

The 'shake test' has, for many years, been our bedside indicator of fetal lung maturity. Clements *et al.* (1972) claimed that this test is rapid and reliable but in our experience it has not proved very successful and management has depended mainly on the L/S ratio and the lecithin concentration of the amniotic fluid.

Because of our reservations about the results obtained with the shake test and because we had some favourable results with the tap test (Socol *et al.* 1984), we investigated the reliability of the tap test and the shake test using the L/S ratio and amniotic fluid lecithin concentration as a standard for comparison. Fetal outcome and associated maternal disease states were not considered as our objective was to determine whether the results of the tap and shake tests were in agreement with the laboratory estimation of L/S ratio and lecithin concentration.

Subjects and methods

Amniotic fluid was obtained from 80 women who had an amniocentesis, as part of their obstetric management, for determination of phospholipid profiles. Informed consent was obtained from each patient. The tap test and the shake test were performed immediately by a single investigator. A further sample of the amniotic fluid was sent to the laboratory for determination of phospholipid profiles. If the phospholipid profile could not be analysed immediately then the amniotic fluid was refriger-

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ated, but all amniotic fluid samples were analysed within 24 h of the amniocentesis. Before undertaking the tap and shake tests, any amniotic fluid contaminated by blood or meconium was spun for 5 min in a centrifuge at 400 rpm. Clear amniotic fluid was not centrifuged.

The tap test was performed as described by Socol *et al.* (1984). This was done by mixing 1 ml of amniotic fluid with 1 drop of 6N HCl, then adding 1·5 ml of diethyl ether. The 16 × 150 mm test tube was tapped briskly three or four times, which created an estimated 200 to 300 bubbles in the ether layer. In amniotic fluid from a mature fetus the bubbles rise quickly to the surface and break down; in amniotic fluid from an immature fetus the bubbles are stable or break down slowly. In our study the tap test was read at 5 min. As recommended by Socol *et al.* (1984), the cut-off for maturity was arbitrarily set at five bubbles. If no more than five bubbles persisted in the ether layer, the test was considered positive. Occasional bubbles confined to the amniotic fluid layer and not dispersed in the ether layer were ignored.

The shake test was performed as described by Clements *et al.* (1972). A test was recorded positive if it showed a complete ring of bubbles in the meniscus of the tube marked 1/2.

The phospholipid profiles were determined by the South African Institute of Medical Research. The L/S ratios were assessed utilizing one-dimensional planimetric thin-layer chromatography after centrifugation for 5 minutes at 3000 *g* and methanol/chloroform precipitation. An L/S ratio of 4:1 or greater was considered indicative of fetal lung maturity (McCulloch *et al.* 1987; Hodge 1973; Gluck & Kulovich 1973). Lecithin concentration was analysed spectrophotometrically using the enzymatic ultraviolet method (Boehringer, Mannheim), a level of 70 µmol/l or greater was considered indicative of fetal lung maturity.

Results

The 80 samples of amniotic fluid consisted of 69 clear specimens, six were slightly stained with meconium and five were contaminated with small amounts of blood.

Of the 80 tap tests performed and read at 5 min, 56 were positive, indicative of fetal lung maturity, and 24 were negative, indicative of fetal lung immaturity. Fifty-one of the 56 positive tap test results were in agreement with the L/S ratio and lecithin concentration but in five the L/S ratio and lecithin concentration indicated lung immaturity. Only 15 of the 24 negative tap test results were in agreement with the L/S ratio and lecithin concentration; in 9 the L/S ratio and lecithin concentration were consistent with maturity.

Shake tests performed on the 80 amniotic fluid samples were positive in 48 and negative in 32. Of the 48 positive tests, 38 agreed with the phospholipid analysis but in 10 the phospholipid analysis indicated immaturity. Ten of the 32 negative results agreed with the phospholipid analysis; in 22 the phospholipid analysis was consistent with lung maturity.

Among the 11 amniotic fluid samples with a 'borderline' L/S ratio of 3·2–3·7, the tap test was negative in six and the shake test was negative in only two.

The results of the tap tests, shake tests and phospholipid analyses are shown in Table 1.

Discussion

No single amniotic fluid test for prediction of

Table 1. Diagnostic efficacy of the tap and shake tests for fetal lung maturity.

Test	L/S ratio, lecithin concentration: Mature	Immature	Total	Positive predictive value (%)	Negative predictive value (%)	Sensitivity (%)	Specificity (%)
Tap test							
Mature	51	5	56				
Immature	9	15	24				
Total	60	20	80	91	63	85	75
Shake test							
Mature	38	10	48				
Immature	22	10	32				
Total	60	20	80	79	31	63	50

fetal lung maturity is completely reliable, easily performed and universally applicable (O'Brien & Cefalo 1980). We found the tap test to be more reliable than the shake test when compared with the phospholipid analysis. The tap test had a positive predictive value of 91% and a negative predictive value of 63% compared with 79% and 31%, respectively, for the shake test. Our determination of a positive predictive value of 79% for the shake test is somewhat higher than that of other authors (Sproule *et al.* 1974; Mukherjee *et al.* 1974). Another major concern is the high rate of false negative test result with the shake test.

The 'borderline' L/S ratio still presents a major problem but better results were obtained with the tap test (six out of 11 negative) than with the shake test (two out of 11 negative) Repeating the tap test and reading the result at 5 and 10 min did not improve the outcome.

We conclude that the tap test read at 5 min is reliable, inexpensive, rapid and technically easy. For clinicians working in peripheral hospitals with limited access to a central laboratory the tap test appears to be a valuable procedure for predicting fatal lung maturity. However, we still consider that where laboratory facilities are available the phospholipid analysis must be preferred until larger scale comparisons which include the clinical outcome of the fetus, have confirmed the reliability of the tap test.

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Cicatricial pemphigoid diagnosed from ocular features in recurrent severe vulval scarring. Two case reports

PEGGY FRITH, MARK CHARNOCK, FENELLA WOJNAROWSKA

Case reports

Patient no. 1

This woman, aged 57 years, had had recurrent irritation, soreness and ulceration of the vulva for 10 years. She had perianal soreness and problems with micturition, being aware of incomplete emptying of the bladder. Fusion of the labia minora had first occurred soon after the onset of symptoms, and had recurred despite four operations to separate the labia. Topical treatment with oestrogen or testosterone had not improved her symptoms. She had no skin or oral symptoms, but said her eyes had felt dry for 2 years. She was hypertensive and had been treated with propranolol 60 mg daily for 2 years.

There was vulval erythema, erosion and scarring with labial fusion. The vagina was stenosed, with anterior and posterior angular cicatrization and narrowing of the urethral orifice. Her skin and mouth appeared normal.

Biopsy of the vulva showed scarring but without the specific features of lichen sclerosus. Tissue immunofluorescence was negative in vulval, forearm skin and lip mucosal biopsies. Circulating antibodies to pemphigus and pemphigoid antigens were not detected.

Ocular examination, using the slit lamp, showed clear evidence of conjunctival scarring, with symblepharon formation in the medial part of the lower lid in the left eye (Figure 1). Schirmer testing showed dryness of both eyes. Conjunctival biopsy for direct immunofluorescence was negative

The patient's symptoms have been partially controlled by topical clobetasol propionate 0·05% to the vulva, and hypromellose eye drops.

Patient no. 2

This 61-year-old woman presented with a similar 15-year history. She had recurrent soreness and ulceration of the vulva, particularly involving the clitoris, with dysuria. She had had two operations to separate the labia, with rapid re-fusion post-operatively, despite topical corticosteroid and oestrogen. For 2 years she had had recurrent oral ulceration involving the lips, tongue, buccal and palatal areas and the pharynx. She had noticed oral blisters occasionally. She also had occasional soreness of the nasal mucosa. Irritation of the scalp, face and ears, without blistering, had been diagnosed and treated as rosacea but minocycline had improved only her nasal symptoms. She also had a 2-year history of recurrent redness and soreness of the eyes, and thought she had noticed blistered areas inside the lower lids. She was also receiving treatment for pernicious anaemia and hypothyroidism.

Examination showed vulval scarring with fusion of the labia, especially around the urethral orifice, and ulceration of the clitoris (Figure 2). There was no evidence of skin or oral scarring.

Cicatricial pemphigoid was suspected because multiple mucosal sites were involved but biopsies of vulval and forearm skin and lip mucosa were negative for immunofluorescence. Circulating antibodies to the basement membrane zone were not detected, and anti-nuclear antibodies were negative. Examination of the eyes did not show clear evidence of ocular scarring but a biopsy of bulbar conjunctiva demonstrated

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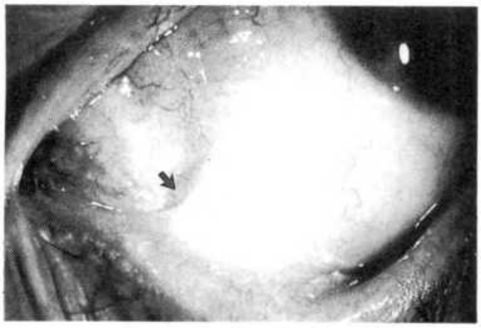

Fig. 1. Patient no. 1. Left lower eyelid everted to show symblepharon (arrowed) with adhesion between tarsal and bulbar conjunctiva.

an unequivocal linear band of IgG deposition at the epithelial-subepithelial junction, typical of cicatricial pemphigoid.

Comment

Collaboration between gynaecologist and ophthalmologist to make a diagnosis must be rare. In our own region, patients have access to a combined clinic for vulval disorders involving a gynaecologist and a dermatologist. Also, because of a research interest in combined skin and ocular disorders, we have realised the importance of ophthalmological assessment including conjunctival biopsy in the diagnosis of cicatricial pemphigoid, as the ocular improvement may be asymptomatic (Venning *et al.* 1987; Frith *et al.* 1989). Two patients were seen in the combined vulval clinic with recurrent vulval ulceration and scarring, and the diagnosis of cicatricial pemphigoid was suspected. Diagnosis was not possible from clinical or histopathological features including tissue immunofluorescence or indirect immunofluoresence for circulating antibodies, until ocular scarring was found in one patient and positive conjunctival immunofluorescence in the other.

Cicatrical pemphigoid, also known as benign mucous membrane pemphigoid, is a scarring condition involving mucous membranes. Affected sites include the eye, mouth, oesophagus, larynx and distal genital tract. Scarring at these sites produces mucosal disorganization and shrinkage. Adhesion between adjacent mucosal surfaces is a particular feature in the conjunctiva and vulva. Believed to be autoimmune in origin, the disorder is chronic and management is difficult. Surgery is in general contraindicated, as rescarring inevitably results.

These two patients are included in a published study by our group of the incidence of involvement of different mucosal sites in cicatricial (scarring) and bullous (blistering) pemphigoid (Venning *et al.* 1987). In the 15 patients with cicatricial pemphigoid, 93% showed oral, 50% ocular, 73% skin, and 47% of the women vulval involvement, either clinical, immunohistological, or both. We noted that ocular signs could occur in asymptomatic patients, and that conjunctival biopsy from a standard site yielded the highest rate of positive immunofluorescence in tissue in comparison with uninvolved skin and lip mucosa, taken from the same patients. The reason for the higher positive reaction in conjunctiva is unknown but we suggest that immunoreactants may be cleared more slowly from this site compared with other tissues. We found conjunctival biopsy to be simple and well tolerated, and acceptable even as a research procedure. The ocular findings in our series and in control patients, and the technique for conjunctival biospy have been described (Frith *et al.* 1989).

The differential diagnosis in patients with vulval scarring and labial fusion includes lichen sclerosus, cicatricial pemphigoid, possibly pemphigus, toxic epidermal necrolysis, and erosive lichen planus (Ridley 1988). Of these only cicatricial pemphigoid, pemphigus and toxic epidermal necrolysis are known to have ocular

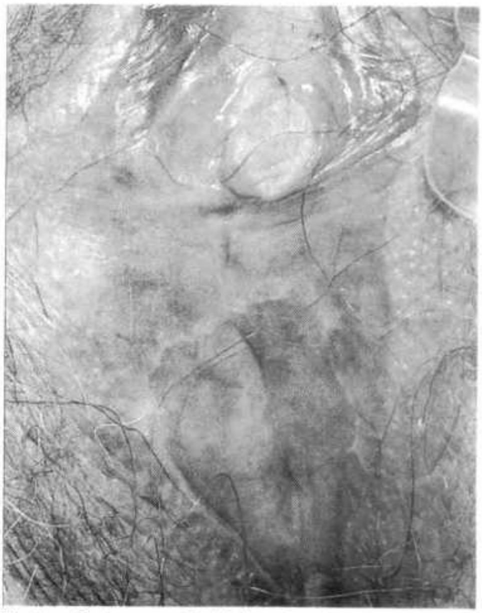

Fig. 2. Patient no. 2. Vulva showing scarring with labial fusion.

involvement, which has a characteristic pattern. These three conditions are distinguishable clinically and on the basis of direct or indirect immunofluroescence. If lupus erythematosus is excluded, we know of no disorder, other than pemphigoid, in which conjunctival immunofluorescence shows a linear pattern at the basement membrane zone.

We believe the association of vulval and ocular features in cicatricial pemphigoid deserves to be more widely known, as it will enable the gynaecologist or dermatologist to offer the patient a clear diagnosis, a prognosis, an awareness of other possible sites of mucosal involvement, and a guide to optimum treatment in which surgery for mucosal adhesions is best avoided.

Acknowledgments

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Transvaginal ultrasound. A reliable basis for clinical management? Case reports

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Case reports

Patient no. 1

A 55-year-old nulliparous woman developed vaginal bleeding 4 years after her menstrual periods had ceased. She was investigated with transvaginal ultrasound using an ALOKA SSD-620 machine, with a 5 MHz vaginal probe givng a 60 degree angle view. The ultrasound scan showed the endometrial thickness to be 3 mm. During the subsequent dilatation and curettage the uterus was perforated and the procedure was abandoned. An immediate repeat scan showed a localized area of sonolucency at the fundus due to bleeding from the site of perforation. She was treated conservatively in view of the ultrasound findings of a normal endometrial thickness, and a repeat scan 6 months later showed a thin endometrium with disappearance of the area of translucency. Vaginal bleeding did not recur.

Patient no. 2

A 74-year-old woman who had had two children had vaginal bleeding 24 years after her last period. She had had a Manchester repair operation for uterine prolapse 9 years before. Transvaginal ultrasound showed an endometrial polyp 20 mm in thickness. Although the cervical stump was palpable clinically, the cervical os could not be identified and dilatation and curettage was impossible. An attempt at hysteroscopy resulted in inadvertent culdoscopy. Based on the scan findings, the patient had a total abdominal hysterectomy and bilateral salpingo-oophorectomy and the presence of an endometrial polyp with no evidence of atypia was confirmed on histology.

Patient no. 3

A 59-year-old nulliparous woman presented with vaginal bleeding 10 years after her last menstrual period. She had a history of breast cancer treated with radiotherapy. Transvaginal ultrasound showed an endometrial polyp 26 mm in thickness. Dilatation and curettage failed to yield any curettings. Because of the scan findings follow-up was arranged. Two weeks after the negative curettage she presented with a malodourous discharge and passage of small amounts of necrotic material. A repeat dilatation and curettage confirmed the presence of a necrotic endometrial polyp.

Patient no. 4

A 69-year-old woman who had had one child presented with recurrent episodes of vaginal bleeding 16 years after her last period. She had a history of breast cancer, and she had had a previous cone biopsy for a CIN III lesion. Two attempts at dilatation and curettage had failed. Transvaginal ultrasound showed an endometrial thickness of 20 mm with a 'hazy' subendometrial halo, an appearance typical of endometrial car-

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cinoma. A recent cervical smear had shown no malignant cells. At laparotomy, which was followed by hysterectomy and bilateral salpingo-oophorectomy, the omentum was found to be encasing the uterus, with pockets of caseous material between them. Enlarged pelvic lymph nodes were also found Histopathological examination of the specimens showed that there was simple endometrial hyperplasia in which were numerous epithelioid granulomas and Langhans giant cells suggesting tuberculous endometritis. The cervix showed an area of CIN III. The lymph nodes were sclerosed and showed reactive changes with no evidence of active tuberculous infection.

Discussion

There is a small group of postmenopausal women in whom a dilatation and curettage or hysteroscopy is technically difficult, and in whom a tissue diagnosis of the cause of vaginal bleeding is therefore not possible. They include patients with stenosis of the cervix or vagina, abnormal pelvic anatomy because of previous gynaecological operations, and those with a history of perforation of the uterus at dilatation and curettage that makes them unwilling to accept the procedure (Hunter *et al.* 1989). The introduction of vaginal ultrasound probes has permitted the use of higher frequency ultrasound at greater proximity to the uterus, resulting in superior resolution (Schwimer & Lebovic 1984). The technique is both accurate (Yee *et al.* 1987) and well tolerated, avoiding the discomfort associated with the transabdominal full bladder procedure.

We report the clinical value of this procedure in four women within a larger study of 93 women with postmenopausal bleeding who were investigated by dilatation and curettage. Each had transvaginal ultrasound scan before curettage as a research procedure to measure the endometrial thickness. In the four patients described here, dilatation and curettage failed and a clinical decision was made solely on the basis of the ultrasound findings with no false positive results. Thus transvaginal ultrasound scan appears to be an appropriate and reliable tool in the clinical assessment of endometrial pathology in postmenopausal women.

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SHORT COMMUNICATIONS

Maternal impressions of forceps or the Silc-cup

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For most couples the birth of their baby is an unforgettable event. Trauma to the mother and baby and maternal pain associated with the delivery can have long lasting psychological sequelae and may influence the decision for further pregnancies or affect the attitude to a subsequent pregnancy.

Several studies have clearly shown that maternal trauma is significantly less with the vacuum extractor than with the forceps (Vacca & Keirse 1989). As part of a randomized controlled trial of vacuum extraction and forceps delivery, Garcia *et al.* (1985) found that women in the vacuum extraction group reported less pain but had more worries about their babies; the views of the medical staff were also surveyed. In our recent two-centre controlled trial comparing the Silc-cup and forceps we found a three-fold increased risk of severe maternal trauma with the forceps although the Silc-cup was associated with a significantly higher failure rate (27%) than the forceps (10%), there was no difference in neonatal morbidity (Johanson *et al.* 1989).

This report concerns the maternal views of perineal pain at delivery and the puerperium, concerns about the baby and their contribution to the delivery.

Subjects and methods

The randomized controlled trial comprised 264 pregnant women divided equally into two groups. Once a woman was entered into a particular group she remained in that group for the purposes of analysis, regardless of the eventual mode of delivery.

Of the 264 women in the study 209 (79%) were interviewed on the third or fourth postnatal day. In this group 102 had been allocated to delivery by forceps and 107 to delivery by vacuum extractor. It was intended that the questions should be asked with the interviewer 'blind' to the mode of delivery.

There was no 'pre-selection' for interview. Of the 55 women not questioned, three were delivered by caesarean section and seven had a normal delivery, most of the others returned home before the third day.

Results

In the forceps group significantly more women found the perineal pain at the time of questioning 'unbearable' and more women reported that the forceps caused 'unbearable' pain at delivery, but this difference was not statistically significant. There was no differences between the two delivery groups regarding worries about instrument marks on the baby (Table 1).

There were no differences in terms of the amount the women felt that they had contributed towards the delivery. Overall, 18% (19/107) in the forceps group and 14% (14/102) in the vacuum extractor group did not understand the reason for the instrumental delivery.

One woman who had experienced a vacuum extractor delivery with a first baby and a forceps delivery for a similar sized second baby (with similar analgesia) found the forceps unbearable and commented that she would request a caesarean section if a forceps delivery was suggested in a future pregnancy. Another woman commented that she did not like the Silc-cup being reapplied.

Discussion

The most important finding was a three-fold increased risk of 'unbearable discomfort' of the

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Table 1. Maternal views on instrumental delivery

Variable	Forceps ($n=102$)	Silc-cup ($n=107$)	Odds ratio (95% CI)
	n(%)	n(%)	
Delivery 'unbearable'	28 (27)	19 (18)	1·75 (0·9–3·4)
Perineum 'unbearable'	18 (18)	7 (7)	3·06 (1·22–7·7)*
Worries about baby	6 (6)	8 (7)	0·7 (0·25–2·3)

* Significant, $P<0{\cdot}05$

perineum on day 3 or 4 in the forceps group. It is also important to note that there was no difference in maternal concern about the baby between the two groups. There was no more concern about the 'chignon' or bruising on the head than there was about forceps marks.

The occurrence of women in both groups who did not know the reason for the assisted delivery emphasizes the need for thorough explanation both at the time of delivery and afterwards.

We felt that the more 'physiological' nature of a vacuum extraction delivery might result in more women feeling that they had made a significant contribution, but this was not the case.

If any woman considers her delivery or perineal discomfort unbearable this is a significant short-coming in service. Adequate analgesia without compromizing maternal and fetal well-being should be possible in nearly all operative vaginal deliveries. Anyone undertaking an operative delivery must make a conscious effort to cause as little trauma and discomfort as possible. Operative deliveries are commonplace for the obstetrician but not for the woman.

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An out-patient approach to the management of post-menopausal bleeding

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Endometrial biopsy is a very safe procedure with Hofmeister (1974) reporting no complications in a series of 20 000 patients. It produces tissue which is satisfactory for histological study with good cellular preservation and nuclear detail (Inglis & Weir 1976). Cytological assessment has the theoretical advantage of being applicable to tiny amounts of material which would be insufficient for histology.

Endometrial cytology has been shown to be reliable in the diagnosis of endometrial malignancy when correlated with curettage, (Isaacs & Ross 1978; Polson *et al.* 1984; Swingler *et al.* 1979) but has not become widely established in clinical practice in managing postmenopausal bleeding (PMB). Although endometrial biopsy is in widespread use for premenopausal menstrual disorders, there has been reluctance to abandon formal curettage under anaesthesia for

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PMB because of anxiety about missing an endometrial cancer.

PMB is a common problem which causes a great deal of anxiety. In our hospital over 400 women with PMB are investigated each year, with around 7% having cancer. An out-patient management protocol would be advantageous in terms of minimizing the need for general anaesthesia, permitting the entire investigation to be completed at one visit thus alleviating anxiety. Furtheremore bed occupancy is reduced, thus helping to trim waiting lists. We have assessed the use of out-patient endometrial biopsy for PMB with the aim of streamlining the management of these patients.

Patients and methods

All patients referred with PMB to Aberdeen Royal Infirmary, but not to a named individual, were seen at a dedicated clinic which was under the supervision of one consultant (H.C.K.). The clinic protocol comprised a full history, and clinical examination, and following informed consent, an endometrial biopsy was attempted using a 3 or 4 mm Karman curette (Rocket). The patient was placed in the lithotomy position with her legs in comfortable supports, The cervix was steadied with a vulsellum and the suction curette, attached to a 50 ml bladder syringe, was gently inserted into the endometrial cavity without dilatation or prior cleansing of the vagina and cervix. Suction was applied and the cavity was gently curetted for a few seconds. Any tissue obtained was sent for histological assessment. If either no tissue or only very scrappy material was obtained the patient was reassured immediately that there was no abnormality. These patients, and those with no histological abnormality, were returned to the general practitioner, who was requested to refer the patient again if there was any further bleeding, when our routine management was dilatation and curettage (D&C). Initially the women were asked to comment on the degree of discomfort they experienced using a linear analogue score.

Results

During the first year 175 patients were seen at the clinic. Almost 70% were between 50 and 70 years of age, and 10% were over 70 years. In five endometrial biopsy was not thought necessary because questioning revealed that there had not been any bleeding. Of the 170 patients in whom endometrial biopsy was attempted the uterus was successfully cannulated in 137 (81%). Of these, no tissue was obtained in 56 (41%) and some tissue, which was frequently very scanty, in which no histological abnormality was present was obtained in 66 (48%). Abnormal tissue was found in 15 (11%). Of these, eight had adenocarcinoma of the endometrium and six endometrial hyperplasia without cytological atypia. One biopsy showed mitotic figures and the pathologist felt that the sample was inadequate to exclude an invasive lesion; a formal curettage was undertaken and the tissue obtained showed no abnormality. The women with endometrial hyperplasia received cyclical progestogens for 6 months after which a repeat endometrial biopsy was performed. In five the endometrium reverted to normal. One woman had a hysterectomy because the hyperplastic changes persisted, but histology of the uterus showed no evidence of malignancy.

In 31 women a D&C was required because endometrial biopsy was unsuccessful, either because of an inadequate speculum examination or more commonly due to an element of cervical stenosis. In two patients initial examination suggested cervical cancer which was confirmed by punch biopsy. Three patients were referred again because of recurrence of PMB, each had a D&C subsequently but no abnormality was detected.

There was no significant morbidity apart from one woman who fainted after the procedure. In no case was the uterus thought to have been perforated. The first 75 patients were asked to comment on the degree of discomfort they felt during the procedure (Table 1). Most felt no or very little discomfort and only 3 (4%) thought that their discomfort was severe. The pain, however, only lasted for a few seconds and the women felt that it was well worth avoiding inpatient treatment.

Table 1. Pain scores on linear analogue scale (1–10) reported by 75 patients undergoing endometrial biopsy

Pain score	*n*	(%)
0–3 (mild)	54	72
4–7 (moderate)	18	24
8–10 (severe)	3	4
Total	75	100

Comment

We have found the pragmatic approach described to be a well tolerated and effective means of managing PMB. By avoiding the need for anaesthesia, in-patient days are reduced and the anxiety associated with waiting time is minimised. Only one in five of the referred patients required further investigation because endometrial biopsy failed but in this group there was one endometrial cancer. Endometrial biopsy detected eight of nine endometrial cancers and did not miss any lesion. None of three women referred a second time because of recurrent bleeding had a significant abnormality identified by formal curettage. We have now investigated 100 women for whom there has been an interval of at least 6 months since the endometrial biopsy and there have been no re-referrals after this length of time. The avoidance of general anaesthesia in many elderly patients may have prevented complications.

This investigation could be undertaken in a general out-patient clinic but our dedicated clinic had several advantages, including adequate equipment, staffing and time. We used a couch with comfortable leg supports to allow the operator adequate access, which was important for some patients. The pathologists generally found the quality of material satisfactory although some samples of endometrium were too scanty for histological assessment. We regarded this as evidence for an absence of intrauterine pathology and did not investigate cytology in such cases. We found endometrial biopsy to be a very simple technique which can easily be taught. We would stress the importance of sensitivity when dealing with elderly women as well as the need for gentleness in undertaking the procedure. A little experience is required to acquire the necessary confidence for maximal success in cannulating the uterus and, although we generally used a 3 mm curette, a 4 mm instrument can also be used and has the advantage of increased rigidity.

We suggest that dilatation and curettage need no longer be regarded as necessary for the investigation of PMB, thus avoiding anaesthesia and reducing waiting time for the large majority of women with no pathology.

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Lesion size and histology of atypical cervical transformation zone

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There are few published data on lesion size in premalignant disease of the cervix. In the same way that lesion size is an important risk factor in other premalignant conditions, it is proposed that the size of lesion in cervical intraepithelial neoplasia (CIN) may be of prognostic significance in its progressive potential. Previous studies have mainly been concerned with sensitivity of cervical screening and its relation to lesion size (Giles *et al.* 1988; Barton *et al.* 1989).

The objectives of this study were to analyse the relation between size of any colposcopic transformation zone abnormality and histology of specimens obtained at diathermy excision of the transformation zone.

Patients, methods and results

All patients referred to the University of Birmingham colposcopy clinic at Dudley Road Hospital from 1 March 1988 were entered into this prospective trial. Two imaginary concentric circles are drawn over the cervix. The outer circle represents the junction of the cervix and the vagina, and the inner circle is halfway between this landmark and the centre of the cervical os. A perpendicular and a horizontal line are also drawn bisecting in the centre of the cervical canal, thereby yielding 8 sectors to the diagram. The lesion size was then assessed according to the number of inner and outer sectors containing colposcopic abnormality and acetowhitening. During an initial pilot study we found good intra- and inter-observer agreement using this technique. If the abnormality within the transformation zone fulfilled the criteria for local ablation, excision was performed using a fine wire loop attached to a Valleylab TM Force 2 Surgical Generator. Specimens were examined without the information on lesion size being included on the histology request form.

Overall, 498 patients were studied. Histology was correlated with the number of sectors involved and the results are shown in Table 1. There was a significant association between number of sectors involved with disease and histological grade ($\chi^2 = 63{\cdot}48$, df = 9, $P<0{\cdot}0001$). The strength and direction of this association was explored using Goodman & Kruskals gamma statistic ($\gamma = 0{\cdot}37$) and testing for trends (Everitt 1977). The linear trend ($\chi^2 = 44{\cdot}4$, df = 1, $P<0{\cdot}0001$) and the curvilinear trend ($\chi^2 = 19{\cdot}03$, df = 8, $P = 0{\cdot}024$) were found by partitioning the overall χ^2 statistic. The γ-statistic shows there is a positive association between histological grade and the number of sectors involved with disease; thus, those with larger lesions tended to have the more severe histological grades of CIN. The trend statistic shows that this association is curvilinear.

Table 1. Relation between sectors and histology in cervical intraepithelial neoplasia

	Cervical sectors involved				
Histology	0–2	3–4	5–6	7–8	
Koilocytosis only	64	32	15	3	114
CIN1 ± koilocytosis	54	36	8	3	101
CIN2 ± koilocytosis	22	39	11	5	77
CIN3 ± koilocytosis	42	97	52	15	206
Total	182	204	86	26	498

Comment

Our study shows a statistically highly significant association between proportion of cervix involved with abnormality and histology of the atypical cervical transformation zone. The size of lesion may be of prognostic significance and have a significant effect on the natural history of preinvasive cervical disease.

An increasing number of patients with abnormal smears are being referred for colposcopic assessment and debate centres on what proportion of those with CIN will progress and over what duration (Jordan 1988). At present we are unable cytologically, colposcopically or histologically to predict which lesions will progress to invasive disease. Our data suggest a need for prospective natural history studies that include and assess our findings, as the progressive potential from low grade to high grade CIN, and thus its progressive potential to invasive cancer, may be related to the size of the lesion. Such a study of minor cytological abnormalities has recently been established in our unit in Birmingham, UK.

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Transient improvement of umbilical arterial waveform after maternal steroid administration. Case report

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We report an observation made during the management of a patient with a growth retarded fetus. She had previously had one first and one second trimester miscarriage, followed by the birth of a macerated stillbirth at term weighing 1·76 kg. In this pregnancy intrauterine growth retardation was confirmed by ultrasonography in the second trimester.

We considered the risk of fetal death very high, and planned delivery as soon as fetal lung maturity was assured. Fetal monitoring was by cardiotocography and umbilical artery flow velocity waveform studies starting from 27 weeks. The Doppler studies were performed using an Aloka SSD630 ultrasound machine equipped with an UGR-38 Doppler unit using the pulsed wave mode. Amniocentesis was first performed at 30 weeks gestation: the lecithin/sphingomyelin ratio was 0·8. Intramuscular dexamethasone (2 doses of 10 mg, 12 h apart) was prescribed to accelerate lung maturation. After the first course of dexamethasone, we noticed a transient improvement in the Doppler waveform. This was also observed following two subsequent courses of dexamethasone. The results of the Doppler studies are summarized in Table 1. There was no change in the basal fetal heart rate as recorded by fetal cardiotocography during the period of these observations.

The lecithin/sphingomyelin ratio reached 2·4 by 35 weeks gestation. A normal 2·2 kg girl was born by elective caesarean section. The umbilical artery and vein pH were 7·30 and 7·34 respectively. The haematocrit at birth was 69·8%.

The umbilical artery Doppler waveform is comparatively constant for a fetus over a short time span (Hastie *et al.* 1988). Changes in the waveform have been reported to be associated with alterations in the fetal heart rate (Van den Wingaard *et al.* 1988), transcutaneous electric nerve stimulation (Kubista *et al.* 1987) and beta-sympathomimetics (Brar *et al.* 1988), but not maternal steroid administration. A recent study by Meizner *et al.* (1989) does not support our observations: there was no change in umbilical artery flow velocity waveform pattern in their patients. Therefore our observation might only apply to certain fetuses under stress.

The effect of maternal administration of steroids on fetal blood flow may be related to a transient accumulation of intermediate steroid metabolites. Some of these metabolites may be channeled into oestrogen synthesis. Meschia (1974) confirmed that oestrogens are very potent vasodilators of the uterine vessels. The vasodilatory effect of exposure to exogenous oestrogens for several seconds lasts several hours. Such vasodilatation is likely to be mediated through protein synthesis, as it is preventable by treatment with cyclohexamide, a protein synthesis

Table 1. Changes in umbilical artery AB ratios after intramuscular maternal steroid administration

Gestation (week)	Timing of FVW measurement in relation to 2nd dose of steroid		
	Before	Within 24 h	After 24 h
31	3·3	2·5 (23 h)	3·5 (48 h)
32	3·1	2·6 (18 h)	3·7 (40 h)
33	n.k.*	2·3 (4 h)	3·1 (44 h)

*The pre-steroid measurement at 33 weeks was missed because of technical problems.

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inhibitor (Meschia 1974). It is possible that oestrogens or other steroid metabolites could similarly cause vasodilatation in the umbilical vessels.

If our observations are confirmed by other studies, they could have important implications in perinatology.

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First trimester CA 125 and Down's syndrome

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In early pregnancy higher levels of maternal serum cancer antigen 125 (MS-CA 125) have been reported to be associated with miscarriage. Check *et al.* (1990) suggested further investigation to see if high levels of MS-CA 125 might be useful for the prediction of fetal chromosomal disorders.

We assessed the value of measuring MS-CA 125 in the first trimester of pregnancy using maternal serum samples from nine pregnancies associated with fetal Down's syndrome.

Subjects and methods

As part of a study of screening for fetal chromosomal disorders we collected maternal sera in the first trimester before chorionic villus biopsy. The serum samples were stored at 20°C. Since 1989, fetal karyotyping has detected nine fetuses with Down's syndrome, four at 9 weeks gestation and five at 10 weeks. Gestational age was calculated from last menstrual period in completed weeks and always confirmed by ultrasound.

To get an impression of the MS-CA 125 levels in pregnancies with chromosomally normal fetuses we matched every sample from the affected pregnancies with three samples from unaffected pregnancies of exactly the same gestational age, to within 3 weeks of storage time and in ignorance of the actual MS-CA 125 values. All the women in the affected and control groups were $\geqslant 36$ years of age. All samples were assayed under code, within one assay run, using the Abbott™ CA 125 enzyme immunoassay.

We used the Mann–Whitney *U*-test to compare the results of the affected pregnancies with the unaffected pregnancies.

Results

In 12 of the 27 unaffected pregnancies the MS-CA 125 level was increased above the

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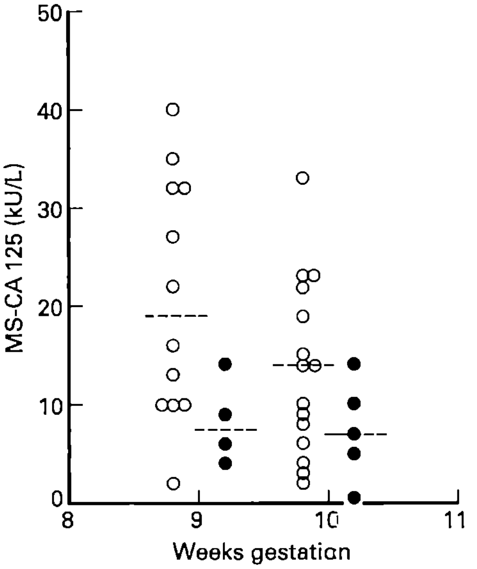

Fig. 1. First trimester maternal serum cancer antigen 125 (MS-CA 125) levels in nine pregnancies affected by fetal Down's syndrome (●) and 27 unaffected pregnancies (○). Median values are shown as dashed lines

normal level for non-pregnant women which is 16 kU/l with our assay.

The values for MS-CA 125 were statistically significantly lower in women with Down's syndrome fetuses than in unaffected pregnancies (Fig. 1). In the affected pregnancies MS-CA 125 levels were 0·39 multiples of the median (MoM) at 9 weeks gestation and 0·50 MoM at 10 weeks. It seems especially worthwhile to investigate the MS-CA 125 levels at or before 9 weeks gestation.

Discussion

In contrast to Check *et al.* (1990) our data suggest that low values of MS-CA 125 may be predictive of fetal chromosomal disorders. It is possible that the high levels reported by Check *et al.* (1990) may have been a result of threatened miscarriage.

Normal endometrial and decidual tissues are a rich source of serum CA 125 during menstruation, when there is endometriosis, after induced abortion or after delivery (Jacobs & Bast 1989). In normal pregnancy, an increase of MS-CA 125 level is seen between 5 and 11 weeks gestation and this then decreases to low levels in the second trimester, remaining low until delivery (Jacobs & Bast 1989; Kobayashi *et al.* 1989). This is probably a result of invasion in the decidua by the trophoblast.

The reason for the low values of MS-CA 125 is not yet clear. The relatively low levels of MS-CA 125 in pregnancies with a Down's syndrome fetus may reflect a less aggressive invasion of trophoblastic tissue but the chromosome abnormality might decrease the production of the CA 125 antigen.

Both explanations are in line with the hypothesis of a dysfunctional placenta as cause for the association between fetal Down's syndrome and abnormal biochemical findings in maternal serum, such as alpha-fetoprotein (AFP), human chorionic gonadotrophin (hCG), unconjugated oestriol (uE3) and pregnancy-specific beta-1-glycoprotein (SP-1) (Merkatz *et al.* 1984; Bogart *et al.* 1987; Canick *et al.* 1988; Bartels & Lindemann 1988). The production (hCG, uE3, SP-1) and the transport (AFP) function of the placenta might be impaired, as well as the invasion by trophoblastic tissue (CA 125).

We are conducting a prospective study to determine if MS-CA 125 could be incorporated in first trimester biochemical screening for Down's syndrome.

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BLAIR BELL RESEARCH SOCIETY

Papers presented at the meeting on 9 September 1990 in Glasgow

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Outcome of ovulation induction by gonadotrophins in clomiphene failure by B. H. Smith, T. C. Li and I. D. Cooke The Jessop Hospital for Women, Sheffield.

Ovulation was induced in 45 anovulatory women in 475 cycles using a 1,3,5-day schedule of human menopausal gonadotrophin (hMG, Pergonal or FSH, Metrodin). Women selected had been treated unsuccessfully with clomiphene citrate after assessment of the endocrine profile and other fertility indicators including male factors. Response was assessed by urinary oestrogen output, ovarian ultrasound and Insler cervical score. Although efforts had been made to control the ovarian response, pregnancy was found to be more likely the higher the peak 24-h urinary oestrogen excretion in response to treatment. A higher Insler score was also more likely to be associated with pregnancy but the size or number of ovarian follicles as assessed by ultrasound was a poor indicator of outcome. No diagnosis of ovulatory dysfunction correlated with a pregnancy rate. Tubal or uterine pathology did not affect outcome nor did semen abnormality, although gross examples had been excluded. Plasma gonadotrophin and testosterone concentrations were not predictive of outcome nor was the presence of treated thyroid disease or hyperprolactinaemia. The outcome of treatment was variable. Overall 20 women (44%) achieved pregnancy. Of the 30 pregnancies 9 (30%) miscarried; this was more likely to occur in women presenting with secondary infertility ($P<0{\cdot}01$). Of the 30 pregnancies, 9 (30%) were multiple, comprising six twin pregnancies and three triplet pregnancies. Again, women with secondary infertility were more likely to achieve multiple pregnancy ($P<0{\cdot}05$). Three of the nine multiple pregnancies miscarried including two of the triplet pregnancies. There was one ectopic pregnancy, which was bilateral. At a price of £8·32 per ampoule of Pergonal and £13·54 per ampoule of Metrodin, the drug cost of treatment was £3637 per baby or £4728 per viable pregnancy. These data are compared with those from other centres.

A new method for assessing the nutritional status of the newborn by D. Burns and T. Wheeler. Department of Human Reproduction and Obstetrics, Southampton University.

Recently the ponderal index has become popular in the assessment of neonatal nutritional status. However, we have found significant differences in the measurement of the length of babies between observers and this detracts from the value of the ponderal index in clinical practice. Recently a simple spectroscopic method of measuring tissue fat has been described. This can be used as an index of adult health and we have assessed its potential in the newborn. Measurements of tissue fat were made at several sites in 20 babies. The most reproducible were obtained from the thigh (coefficient of variation 5·5–5·9%). Comparisons among 80 other babies showed that tissue fat was significantly correlated to other indicators of nutritional status including the ponderal index, head/mid-arm circumference ratio and skinfold thickness. The best correlation was with skinfold thickness (0·79) It is known that most of the fat deposition occurs in the latter part of pregnancy and that 80% is found in the subcutaneous tissues. 'Near infra-red' spectroscopy may offer a simple, quick and reproducible way of measuring this and providing a guide to those babies whose stores are reduced.

Haemodynamics of hypertensive pregnancy by S. MacPhail, S. Hunter and W. Dunlop. Princess Mary Maternity Hospital, Newcastle upon Tyne.

The haemodynamic changes associated with the development of pregnancy induced hypertension (PIH) remain unclear because of the inclusion of parous women who had received either medication or intravenous therapy before haemodynamic assessment. Measurement involving invasive techniques makes comparison with normal pregnancy impossible. Cardiac output (CO) was measured by the combined non-invasive techniques of echocardiography and Doppler ultrasound. Blood pressure (MAP) was measured by sphygmomanometry and the total peripheral vascular resistance (TPVR) was calculated. This technique has been previously validated in our department for use in pregnancy. We measured the CO in 36 primagravid women who developed PIH and were not on therapy; 24 women had significant proteinuria (>0·3g/24 h or +++ on dipstick testing). They were matched for gestational age with 36 normotensive primigravidae who had an uneventful pregnancy. The results are shown in Table 1.

In untreated hypertensive pregnancy there was no significant change in cardiac output when compared with normotensive women at the same gestation and there was no haemodynamic difference between proteinuric and non-proteinuric PIH. However, TPVR was significantly elevated and would appear to be the underlying haemodynamic abnormality in pregnancy induced hypertension.

Biophysical fetal assessment. Criteria and outcome by D. A. J. Sim and J. C. Dornan. Department of Obsterics and Gynaecology, Queen's University of Belfast Institute of Clinical Science, Grosvenor Road, Belfast BT12 6BJ.

Biophysical fetal assessment is an established means of surveillance for pregnancies identified as high risk. An abnormal biophysical profile score is an uncommon finding associated with poor fetal outcome. This study was based on 662 patients, referred for fetal assessment, in terms of fetal growth, amniotic fluid volume, biophysical profile score and outcome. Amniotic fluid was reduced in over 20% of examinations. A similar percentage had a reduced abdominal circumference but only 2% of examinations gave an abnormal biophysical profile score. Amniotic fluid volume, abdominal circumference and biophysical profile score all showed highly significant correlations with neonatal size and morbidity. The sensitivity of abdominal circumference for small for gestational age (SGA) was 85%. Five of the six deaths were preceded by a reduced amniotic fluid volume. The success of fetal assessment depends on identification of the fetus at risk. Antenatal care in our unit detected only 27·5% of SGA infants and four unsuspected SGA fetuses died *in utero*. The negative predictive value of amniotic fluid volume for perinatal mortality is 99·8% and abdominal circumference for SGA 97%. Ultrasound assessment of amniotic fluid and abdominal circumference at each antenatal visit should correctly identify the fetus at risk.

Table 1. Haemodynamic characteristics

			PIH					
Variable	Normotensive (*n*=36)		All (*n*=36)		Proteinuric (*n*=24)		Non-proteinuric (*n*=12)	
MAP (mmHg)	90	(1·2)**	111	(1·3)	113	(1·8)*	107	(1·4)
Aortic area (cm^2)	3·9	(0·09)*	3·6	(0·1)	3·6	(0·1)	3·6	(0 1)
Velocity integral (cm)	21	(0·4)	22	(0·6)	22	(0·7)	21	(1)
Stroke volume (ml)	82	(2·4)	79	(3·3)	81	(4·5)	74	(4)
Heart rate	84	(1·7)	81	(2·2)	79	(2·9)	86	(2 9)
CO (l/min)	6·85	(0·2)	6·36	(0·3)	6·34	(0·4)	6·4	(0·4)
TPVR (dyne.sec.cm^{-5})	1083	(38)**	1522	(103)	1586	(146)***	1394	(97)

Significance of difference: normotensive *vs* PIH. $^{*}P<0{\cdot}05$, $^{**}P<0{\cdot}001$; proteinuric *vs* non-proteinuric $^{***}P<0{\cdot}01$

Antepartum fetal response to vibro-acoustic stimulation by J. A. D. Spencer, A. Deans, P. Nicolaidis and S. Arulkumaran. RPMS Institute of Obstetrics and Gynaecology, University of London, Queen Charlotte's & Chelsea Hospital, London W6 0XG.

Fetal heart rate (FHR) response to vibro-acoustic stimulation was recorded in 52 inpatients, between 36 and 41 weeks gestation, who reported normal fetal movements. All FHR records were made in the morning. Vibro-acoustic stimulation was applied during low FHR variability in 25 pregnancies and during high FHR variability in 27. In 10 women from each group a complete rest-activity cycle (consecutive episodes of low and high FHR variability), obtained from a long FHR record the previous morning, was compared with a complete cycle obtained from the record following stimulation. In all pregnancies the initial FHR response was a rise in rate (acceleration/transient tachycardia) lasting between 1 and 15 min (mean amplitude 33·4, SD 7·9 beats/min and mean duration 4·8, SD 3·0 min when stimulated in low FHR variability; mean amplitude 37·4, SD 9·2 beats/min and mean duration 6·3, SD 3·2 min when stimulated in high FHR variability; Wilcoxon's two-sample tests not significant). In all pregnancies, the FHR continued in high variability until cycles resumed (mean durations 37·6, SD 25·7, and 51·6, SD 30·9 min respectively; Wilcoxon's two-sample test not significant). In the 20 pregnancies studied on two occasions, the next complete cycle of low and high FHR variability episodes was not significantly different from that seen on the previous day, irrespective of variability at the time of stimulation. Thus, vibro-acoustic stimulation produces an acute, transient, rise in the FHR followed by persistence of high variability. Disruption of the rest-activity cycle, seen after vibro-acoustic stimulation in low variability, does not extend to the next cycle.

Randomized controlled trial of antenatal day care versus routine care in non-proteinuric hypertension in pregnancy by D. J. Tufnell, P. C. Buchan and R. J. Lilford. St James's University Hospital, Leeds.

Fifty four women in the third trimester of pregnancy with either a diastolic blood pressure between 90 and 105 mmHg and/or a systolic blood pressure between 150 and 170 mmHg were randomized by computer to either day care ($n=30$) or routine care ($n=24$). Exclusion criteria were proteinuria or previous admission in index pregnancy for hypertension. The day care group were managed by a set protocol described by J. J. Walker in the Proceedings of the 16th Study Group of the RCOG. The control group were managed as prior to the setting up of the unit. This did not necessarily imply admission. There were fewer induced labours in the day care group (26·7% *vs* 65·2%, $P<0{\cdot}001$) and they spent less time in hospital (mean 1·1 SD 2·6 *vs* 5·1 SD 4·3 days, $P<0{\cdot}001$), but they had more hospital visits (mean 8·6 SD 2·1 *vs* mean 7·1 SD 1·5, $P<0{\cdot}05$). There were no measurable differences in obstetric outcome. A follow-up postal questionnaire showed no difference in satisfaction with antenatal care but in 15 or 45 replies an unprompted comment stated they preferred more outpatient care. In the next pregnancy 97% would attend twice a week to avoid admission and 37% were prepared to attend every day.

The management of hyperandrogenism with GnRH agonist therapy by Z. M. Van der Spuy, F. A. Nugent and S. Mahabeer.* Dept. of Obstetrics and Gynaecology, University of Cape Town Medical School, Cape Town, and *Dept. of Chemical Pathology, University of Natal, Durban, RSA.

Women presenting with hirsutism secondary to the polycystic ovarian syndrome were treated either with the GnRH agonist analogue Zoladex (goserelin 3·6 mg) plus Diane 50 (cyproterone acetate 2 mg, ethinyl oestradiol 50 µg daily for 21 of 28 days) or with Diane 50 alone. The initial assessment of these patients included the estimation of adrenal and ovarian function and glucose tolerance tests. Therapy was continued for a minimum of 28 weeks. To date 21 women have been recruited to the study and 11 have completed the initial 28 weeks of therapy. Testosterone, androstenedione and DHEAE were suppressed and SHBG concentrations elevated during therapy in both groups. Women who received treatment with goserelin had a significantly lower free androgen index than those in the Diane only group. Hair growth and sebum production were inhibited in both groups. However, by the end of a year of treatment, the women who had completed 56 weeks of therapy with goserelin demonstrated a greater inhibition of hair growth. A possible role for GnRH agonist therapy in the management of hirsutism secondary to polycystic ovary syndrome is suggested by these studies.

Catheter drainage following radical hysterectomy for cervical cancer—urethral or suprapubic catheter? by D. J. Walsh. Stobhill General Hospital, Glasgow.

Thirty-seven patients who were to undergo radical hysterectomy and node dissection for cervical carcinoma in the year March 1989–February 1990 were randomized in a study to compare continuous post-operative bladder drainage by suprapubic and urethral catheters. Two of these patients were later excluded from the study. Of the 35 patients who completed the study 21 had urethral, and 14 suprapubic catheters. The average duration of catheter drainage in 21 patients before return of spontaneous voiding was 17 days (ranges 5–63, median 7). There was no difference in duration of continuous drainage between the two groups. There was no significant difference in the frequency of urinary tract infection between the two groups, infection occurring in 76% of patients with urethral catheters, and 69% in those with suprapubic catheters. Most patients found their catheters comfortable and would use them again, irrespective of type. In terms of ease of nursing and timing of return of spontaneous voiding, however, the suprapubic catheter was found to be preferable.

Atrial natriuretic peptide: a regulator of the fetoplacental circulation?—evidence from intravascular transfusion therapy by J. Kingdom, G. Ryan, J. Doyle,* J. Connell,* R. Morrow, M. McNay and M. Whittle. Perinatal Vascular Research Group, The Queen Mother's Hospital & MRC Blood Pressure Unit,* Glasgow.

That the human fetus can cope with an acute transfusion of perhaps 50% of its circulating blood volume is remarkable. The mechanism(s) involved remain unclear, but could perhaps involve dynamic alterations in the placental vasculature. Atrial natriuretic peptide (ANP), a 28 amino acid peptide secreted by the heart in response to atrial stretch may have a role in the control of fetoplacental vascular tone, as recent work has shown that it can counteract the vasoconstrictor effect of angiotensin II in the perfused human placental cotyledon. Though the physiology of ANP as well characterized in the adult, several groups have now shown the presence of ANP in the fetal circulation, and specific binding sites have been demonstrated in the fetoplacental vasculature. The aim of this ongoing study is to investigate the change in fetal ANP in response to intravascular transfusion therapy. More recently, we have been measuring the systolic/diastolic (S/D) velocity ratio changes in reponse to transfusion in the umbilical, aortic and middle cerebral circulations, in an attempt to define any changes in the distribution of blood flow within the fetoplacental circulation. Paired samples of maternal and fetal blood (before and after transfusion) were collected on ice into EDTA/Trasylol tubes, separated and stored at −20°C. ANP was measured by a pre-extracted radioimmunoassay developed at the MRC Unit. Pulsed Doppler waveform measurements were made before transfusion, within 20 min of completion, and on two more occasions within the next 24 h. Though there was a wide variation in ANP concentration before transfusion (range 4–86 pmol/l), in 13 of 15 patients fetal ANP rose in response to transfusion ($P<0{\cdot}05$ Wilcoxon rank). Before transfusion fetal ANP values were individually higher than the corresponding maternal ones. Doppler flow velocity waveforms have been recorded in association with six transfusions. There appears to be an acute reduction in the systolic/diastolic ratio following transfusion in the three vessels studied, and the ratio returns to pre-transfusion values within 24 h. These preliminary results demonstrate a release of fetal ANP in response to acute intravascular volume loading. The accompanying transient changes in Doppler systolic/diastolic ratios suggest a reduction in peripheral vascular resistance which could assist the fetus in coping with this stress. This project is funded by the Medical Research Council.

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CORRESPONDENCE

Early identification of placenta praevia

Dear Sir,
We are very pleased to have seen this paper by McClure and Dornan [*Br J Obstet Gynaecol* (1990) **97**, 959–961]. The findings were similar to the ones we found from our investigations. We are, however, rather disappointed that McClure and Dornan did not separate the anterior from the posterior low-lying placentas. We would like to emphasize the need for this particular classification as we found in our patients with placenta praevia that at term those with a posterior low-lying placenta did not show 'placental migration' as was seen in those with an anterior low-lying placenta. This confirmed an earlier observation by Macafee *et al.* (1962) that in most women with placenta praevia the low-lying placenta was posterior. We therefore reiterate the point made at the end of our paper (Ruparelia & Chapman 1985), that re-scanning after the early detection of a low-lying placenta should be restricted to those with a posterior low-lying placenta, and also those who bleed during their antenatal period.

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Fish-oil and pre-eclampsia

Dear Sir,
We read with interest the informative commentary by Niels Secher and Sjurdur Olsen [*Br J Obstet Gynaecol* (1990) **97**, 1077–1079], however, recent work suggests a possible relation between fish-oil supplements and pre-eclampsia that was not mentioned in the commentary.

Platelet angiotensin II (AII) binding sites have been found to be increased in patients with pre-eclampsia compared with normotensive primigravidae (Baker *et al.* 1989, 1991a), and the level of platelet AII binding has been shown to correlate with AII pressor sensitivity, known to be increased in pre-eclampsia (Gant *et al.* 1973; Baker *et al.* 1991b).

A possible mechanism by which platelet AII binding is increased in pre-eclampsia was suggested by Gleeson *et al.* (1990), who suggested that the platelet membrane in women with pre-eclampsia has an inherited or acquired defect, perhaps due to a change in phospholipid content ratio and glycocalyx structure on the surface of the platelet membrane, which causes an increase in viscosity. It is believed that alterations in cell membrane fluidity can affect the accessibility of cell membrane proteins which act as binding sites. Increasing the viscosity of a cell membrane decreases its capacity to solubilize integral proteins, displacing the proteins toward the aqueous phase on either side of the membrane (Borochov & Shinitzky 1976). This 'vertical displacement' of membrane proteins may thus allow previously concealed binding sites to be unmasked. In a small pilot study, Gleeson *et al.* (1990) found significantly higher platelet membrane viscosity in patients with pre-eclampsia than in normotensive controls.

In addition to inhibiting platelet aggregation, dietary n-3 polyunsaturated fatty acids are known to decrease platelet membrane viscosity (Van Dias *et al.* 1982). This may thus be associated with a diminution in AII binding sites, which would reflect the reduction in AII pressor sensitivity consequent upon fish-oil intake, mentioned by Secher & Olsen.

Measurement of platelet AII binding sites has been suggested as a possible screening test for pre-eclampsia (Baker *et al.* 1991a&b). A prospective study examining the efficacy of administering fish-oil supplementation to women with high values of platelet AII binding in reducing the occurrence of pre-eclampsia, and assessing the effect of fish-oil supplementation on platelet AII binding, would be of value in further unraveling the complex disease process.

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Hormone implants and tachyphylaxis

Dear Sir,

Garnett *et al.* [*Br J Obstet Gynaecol* (1990) **97**, 917-921] state that no data are currently available to suggest that the supraphysiological oestradiol levels in postmenopausal women after oestradiol implantation are deleterious. However, the incidence of thrombo-embolism correlates with oestrogen dosage in women who use oestrogen contraceptives (Bottiger *et al.* 1980), especially women aged over 35 and those who smoke (Mannen 1982). Moreover, postmenopausal oestrogen therapy has been reported to depress levels of the physiological anticoagulantantithrombin III, and this effect is dose dependent (Gordon *et al.* 1988).

We wish to report the preliminary results of a current study which suggests that supraphysiological levels of oestradiol in such women are indeed associated with hypercoagulability. Prothrombin fragment F1+2 is a specific and sensitive marker of prothrombin activation, which permits estimation of factor Xa activity and in-vivo thrombin formation (Bauer & Rosenberg 1987; Boisclair *et al.* 1990). We measured the

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plasma levels of fragment F1+2 in 12 postmenopausal women with oestradiol implants, and in 7 age and weight matched postmenopausal controls, using an ELISA assay (Behring, Magdeburg).

Eight of 12 (67%) patients with supraphysiological oestradiol levels (serum oestradiol >1200 pmol/l) were found to have pathological elevation of plasma fragment F1+2 (mean 1·18, SD 0·44 nmol/l, range 0·59–2·22 nmol/l; reference range: 0·5–1·0 nmol/l, median 0·73 nmol/l). Plasma F1+2 levels in the hormone-replacement group were significantly higher than those found in the control group ($P<0{\cdot}01$), whose plasma F1+2 levels were invariably normal (mean 0·74, SD 0·12 nmol/l, range 0·53–0·94 nmol/l).

This suggests that significant prothrombin activation and a prethrombotic state occurs in association with these supraphysiological oestradiol levels. Caution must therefore be exercised when treating women with serial oestradiol implants.

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Dear Sir,

The definition of supraphysiological hyperoestrogenism, >1750 pmol/l, used by Garnett *et al.* [*Br J Obstet Gynaecol* (1990) **97,** 917-921], conceals the true incidence of the development of unphysiologically high concentrations of oestradiol as a result of hormone replacement therapy (HRT) by implant. According to Collins (1986), the mean concentration of oestradiol between the 11th and 20th days of the normal menstrual cycle is 478 pmol/l (SD 450). If the mean ±2 SD value is used to define normality, levels of over 978 pmol/l should be considered supraphysiological. The cut-off point used by Gangar *et al.* (1989) is therefore more appropriate. Using this cut-off point, over 16% of the women described by Garnett *et al.* had supraphysiological hyperoestrogenism. In a recently completed prospective study of 38 patients receiving implants at All Saints' Hospital, Chatham, 24% were found to have this degree of hyperoestrogenism. The mean was 738 pmol/l (SD 485).

Whether supraphysiological hyperoestrogenism represents pathological hyperoestrogenism remains a moot point, but even the tentative suggestion of psychopathology in Garnett's study requires the support of the finding of a lower incidence of psychological disturbance in their patients with 'physiological' levels of oestradiol. They did not.

In a recent telephone survey of all hospitals in the South East Thames Region, I found only one in which the pre-implantation level of oestradiol was assessed routinely. With this degree of underinvestigation, any deleterious effect of hyperoestrogenism following implant therapy is unlikely to come to light.

The importance of pre-implantation assessment is that it enables us to counsel the hyperoestrogenic patients and to review with them the primary indication for HRT.

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Authors' reply

Dear Sir,

Thank you for the opportunity to reply to these two letters. It should be well understood that one cannot extrapolate combined oral contraceptive data on clotting to hormone replacement therapy (HRT) using oestradiol. Oral contraceptives use synthetic oestrogens with continuous progestogens and undoubtedly have a depressant effect upon antithrombin III. Oestradiol, as used in HRT for the menopause, does not produce clotting changes (Notelovitz & Ware 1982).

In our clotting study (Studd *et al.* 1978) on various oestrogens and progestogens, we reported two coagulation factors, two indices of fibrinolysis and four measurements of platelet behaviour, we found no changes with natural oestrogen but minor changes only with the progestogen ethynodiol diacetate. We are currently investigating women, who have high oestradiol levels after hormone implantation, with a profile of 15 coagulation assays, again in collaboration with Professor Vijay Kakkar. It would be wrong to draw any clinical conclusions from any study using inadequate indices of coagulation but we agree that a detailed study needs to be done.

Of the 38 women with supraphysiological oestradiol levels 40% smoked heavily and 70% had a uterus and therefore were receiving cyclical progestogens for 10 days a month. These two factors will affect coagulation variables. I would urge Dr Yoong and colleagues to investigate women who have had a hysterectomy, who are non-smokers, have not received testosterone, are not taking progestogens and preferably are not on psycho-active drugs.

Our reasons for choosing 1750 pmol/l as a cut-off value were discussed in our paper. It is commonplace to find random levels of 1250 pmol/l or more in pre-menopausal women. Even so, it is true that this would be an underestimate as blood samples were taken at the nadir rather than at the peak of implant activity. Whatever level is used, the question remains whether this high level is hazardous, or without risk, or whether high oestradiol levels are necessary for the correction of severe osteoporosis or severe peri-menopausal depressive disorder in certain patients. We believe that this high level is beneficial, as we have shown that the incremental increase in vertebral bone density after a year of implants is directly related to the levels of oestradiol achieved (Studd *et al.* 1990).

We believe that the women who develop high oestradiol levels with repeat implantation are those with depression, premenstrual syndrome or even those with an addictive personality, such as the heavy smokers, who come for repeat implants when they are no longer feeling as well as last week! Much of the problem is one of expectation in that these women demand a greater response than is reasonable.

We are delighted that Dr Kabukoba's telephone survey of South East Thames Region hospitals found only one group who tested for pre-implantation levels of oestradiol. We wish he had found none. It is not necessary. It is a waste of money and resources as the oestradiol levels will virtually always be in the normal range even at the return of symptoms (Cardozo *et al.* 1984). If too great a dose is being inserted too often, plasma oestradiol levels can be estimated but not as a routine measure. Even then it is hard to know how to interpret the information. We would stress that the correct dose of subcutaneous oestradiol as an implant for relief of menopausal symptoms is 50 mg oestradiol inserted every 6 months (Studd *et al.* 1978), 75 mg may be required for correction of osteoporosis (Studd *et al.* 1990) and 100 mg may be required, but rarely, for severe premenstrual or climacteric depression (Magos *et al.* 1986; Montgomery *et al.* 1987).

Repeated oestrogen implants clearly have a cumulative effect as shown by Cardozo *et al.* (1984) and Savvas *et al.* (1988). The prolonged effect of an implant was shown long ago by Hunter *et al.* (1973); Thom *et al.* (1981) and Cardozo *et al.* (1984). There are advantages of such high and prolonged levels and we have no doubt that hormone implants are the treatment of first choice in patients without a uterus because of their efficacy, simplicity and safety. The possible side-effects are speculative but are the subject of long term investigation in this unit.

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BOOK REVIEWS

Perinatology Hematology (Methods in Hematology) edited by Blanche P. Alter. Churchill Livingstone, New York, Edinburgh, London 1990. 265 pages with figures and tables, £40.00

This book is one of the most recent in a series concerning Laboratory Methods in Hematology and as such will be primarily of interest to clinical and laboratory haematologists. However, Blanche Alter has gathered together a group of distinguished authors from both sides of the Atlantic, including obstetricians and paediatricians as well as haematologists, all of whom are actively involved in the practice of perinatal medicine.

The first chapter by Rodeck & Nicolini is a masterly overview of the obstetric approaches to fetal haematology. It is packed with information regarding examination of the fetus and fetal tissue sampling for the prenatal diagnosis of genetic and acquired haematological disorders.

Subsequent chapters deal with laboratory methods of prenatal diagnosis of haemoglobinopathies and of haemostatic disorders using both DNA analysis and examination of fetal blood.

The lucid informative chapter on fetal red cell alloimmunization by Nicolaides & Miboshan will be of interest to any obstetrician in hospital practice. This is a rapidly diminishing problem following prophylaxis with anti-D immunoglobulin and knowledge and expertise outside special centres is lacking to deal with the rare remaining cases.

The rest of the book is devoted to haematological disorders in the neonate. There are three chapters dealing with recognition and investigation of red cell disorders, coagulation disorders and leukocyte abnormalities.

The last two chapters deal with the very rare complications of perinatal aplastic anaemia and neoplasia.

This will be a valuable reference text for anyone concerned with fetal and neonatal haematology and particularly for anyone involved in perinatal medicine who wishes to embark on haematological research.

To quote from Blanche Alter's Preface: 'We hope that readers will come to understand how specimens are obtained from fetuses and infants, how the laboratory tests are miniaturized and performed and how the results are interpreted within a narrow age range. The perinatal period is clearly unique in many ways and if this volume enhances at all our ability to deal with the haematologic problems of this period then its purpose will have been served.'

Elizabeth Letsky

Clinical Infection in Obstetrics and Gynecology edited by Allan B. Maclean. Blackwell Scientific Publications, Oxford, Edinburgh, London, 1990. 392 pages with figures and tables, £39.50

A varying level of success is achieved in this book's ambition to cover the whole of the field of infection in obstetrics and gynaecology in less than 400 pages.

The obstetric section is the better. There is an entertaining historical review, and excellent sections on HIV, tuberculosis and listerosis. Coverage of other bacterial and virus infections is adequate but sometimes rather scanty. For example, herpesvirus infections in pregnancy occupies only three pages but tuberculosis occupies 17. And should the chapter on chlamydial infection not deal with *Chlamydia psittaci* as well as *C. trachomatis*?

Weaknesses appear in the section on gynaecology. A valiant but unsuccessful attempt is made to cover the whole of genito urinary medicine in 17 pages. In contrast, the accounts of specific subjects such as surgical infection, antibiotic prophylaxis, infertility and urinary infection are sound and helpful. The section on pelvic inflammatory disease expresses highly traditional views. No mention is made of laparoscopic grading, modern diagnostic aids, pelvic pain syndrome or internationally recommended treatment schedules, and the concept of chronic disease is accepted without question. Apart from mention of newer antibiotics this section acknowledges none of the large amount of research published in the past ten or more years.

The root of the book's weakness is in the author selection. Twenty-six of the thirty-one work in Scotland; did the remainder also work there at some time? By limiting his recruitment of authors by geographical area Dr Maclean took a significant risk, and has produced a book of very uneven quality. I would buy it for its good parts—not its bad!

John Hare

Obstetric Genetics by Zoltán Papp. Akademiai Kiado, Budapest, 1990. 220 pages with figures and tables, $69.00

Obstetric Genetics is one of those chimaeric books that takes the front end of one discipline and tacks it onto the back end of another to produce a creature in search of a *raison d'etre.* Theoretically there are an infinite number of permutations of these animals (obstetric biochemistry, biochemical geriatrics, geriatric obstetrics, etcetera) and it is important to ask, each time they make an appearance, what they are trying to achieve. In the present case, is the aim to cover 'All you need to know' in genetics for the obstetrician or to provide a guide on 'What to do until the geneticist arrives'? In the former case one might ask the question, 'is this book as good as (or better than) having a geneticist on the end of a phone?', in the latter, 'will this book stop me making a fool of myself until I refer on?'

There are eighty chapters (some only a page or two long) covering basic genetics, prenatal diagnosis, screening and treatment, practical, psychological and ethical aspects of genetic counselling and the full range of genetic and teratogenic conditions.

The section on basic genetics is thorough and factually correct. The problem is that these types of introductory chapters, written by well-versed experts, can turn into a liturgy unless a great deal of imagination and effort is put into the presentation. Here the chapters are 'sound' but the line-drawings are old fashioned and the text too succinct. I wouldn't like this to be my first introduction to genetics since medical school.

The chapters on prenatal diagnostic techniques are extremely short—for example fetal blood sampling gets a page of text and a table of conditions where the technique might be used. In contrast amniofetography gets the same anount of space.

The chapters are liberally endowed with references, but these are carpet-bombed on the reader rather than laser-guided. None of them is cited in the text, which gives the impression that, although the author has obviously read them all, he did not refer back to them when writing the chapter. This is unfortunate because the information is factually correct, but comes across as somewhat anecdotal. There are tables of different types of genetic conditions, but these are unhelpful as the conditions are not described in any detail or individually referenced and are arbitrarily selected. The chapter on 'Monogenetically determined multiple malformation syndromes' is a case in point. It consists of less than a quarter of a page of text and a table giving a one line summary of twenty-five of the more than a thousand multiple malformation syndromes. Varadi-Papp syndrome appears here, which is fair enough, but it is extremely rare and overlaps with the much more common Joubert syndrome, which is not mentioned at all. (Incidentally, the original report was by Varadi, *Szabo* and Papp—Varadi and Papp are husband and wife—it looks like they all rolled over and Szabo fell out.)

This is a noble effort to produce a comprehensive text on genetics for obstetricians. It seems cheap for the quality of production, but the author has been too ambitious and as a result the coverage of each subject is far too superficial. The obstetrician who wants to know more about basic genetics would do better buying one of the many excellent introductory texts (e.g., Connor & Ferguson-Smith or Gellerher & Collins) and, for clinical problems, investing in Harper's 'Practical Genetic Counselling'.

Robin Winter

Medical Statistics on Microcomputers by R. A. Brown & J. Swanson Beck. British Medical Journal, London, 1990. 103 pages, with figures and tables, £8 95

This volume is a collection of articles written by a mathematician and a pathologist for the *Journal of Clinical Pathology* and is directed primarily at laboratory scientists with little knowledge of statistics. Its unique aim is to describe common statistical techniques without the use of algebra, this being taken care of by the statistical packages Statgraphics and Minitab. The authors partially succeed and, in a way, it is refreshing to read a statistics book unencumbered by equations; sometimes, however, one feels that understanding would be enhanced by algebra. One of the strengths of the book is the emphasis on estimation and confidence intervals rather than significance testing; furthermore it gives clear guidance on the statistical method appropriate to a particular investigation, and also the limitations of the statistical technique. The chapter on the principles of linear regression and correlation and their pitfalls is particularly good. There are 48 figures most of which are dot plots, box-and-whisker plots and scattergrams which clarify the text greatly; the figures of the computer outputs however are sometimes confusing.

But often the description of the statistical methods is inadequate or hard to follow. Standard deviation is defined as 'the square root of the average of the squared deviations of the data values from the mean'. True enough, but difficult to understand without several readings of the text, and how much easier to grasp if algebra were used (after all algebra is the symbolic representation of abstract thought). To the uninitiated the section on analysis of variance must be a struggle: 'The method uses (a) the variance of the set of sample means and (b) an estimate of the natural variability based on the variances of the responses in each group, known as the "pooled" within groups variance, to calculate the variance ratio, or F ratio, which is merely (a) divided by (b)'. Quite so, but in my experience the best way to understand analysis of variance is to work through an example, using algebraic symbols. The figures of the computer outputs are sometimes daunting: for example the Statgraphics output for a two-sample *t* test shows 25 numerical values, culminating in an abbreviated discussion of the null and alternative hypotheses which for the newcomer to statistics may be difficult to comprehend without an explanation in the text of the difference between the null and alternative hypotheses (there is no such explanation).

It is a pity that the book is directed to laboratory scientists since the title will attract clinicians who are working towards a thesis who may not have access to a university computer and who may purchase their own microcomputer. Some information on computer hardware would have been very helpful. Furthermore only two statistical packages are considered; what about BMDP, Genstat, Nanostat, P-STAT. SPP, and SPSS? There is no information on the cost of the packages, availability, 'user friendliness', the statistical tests available, and the quality of the tables and graphics; for example Minitab is very 'user friendly' and can cope with all of the commonly used statistical tests, but it cannot perform some less common tests such as unbalaned 2-way analysis of variance, non-linear regression, survival analysis or logistic regression, and its graphic facilities (even higher resolution) are not wonderful.

The main problem with this book is that it cannot make up its mind whether to be a book on statistics or a book on computers, and ends up being somewhere in between. It will be useful as a starting point for the clinician completely new to statistics who must then augment his knowledge with a more detailed textbook of statistics.

J. M. Grant

Clinical Practice of Gynecology, Vol 1 No 2, Papillomavirus Infections edited by Barbara Winkler & Ralph M. Rickhart. Elsevier Science Publishing Co., New York, Amsterdam, London, 1989. 259 pages with figures and tables, $35.00, D fl 90

The human papillomavirus is a ubiquitous infection which has become gradually of more interest in increasing numbers of medical specialties. Its importance in the causation of clinical cancer is still widely debated. In order to keep up to date with such a topic, there is a need for a clearly written, authoritative monograph which interested or involved clinicians can use for reference. Clinical Practice of Gynecology is a series of monographs edited by Dr Michael Baggish and produced in the United States of America. Volume 1, No 2 (1989) is devoted to the subject of human papillomavirus infections and is edited by two world authorities, Barbara Winkler and Ralph Rickhart. They have collected an international list of contributors to produce an excellent review which is well written, clearly illustrated and fully referenced. As the title of the series suggests, this is not just a series of chapters on the theory of HPV infection, diagnosis or natural history, but is clinically orientated, discussing the changes in the man, woman and in the baby and child. Advice is given on the management of the infection, both in the adult and antenatally and postnatally.

The problem with such a topic is that time rapidly alters the information available, as research increases knowledge of the natural history and management of the disease. For example, the polymerase chain reaction is mentioned but only in passing, although this technique is now proving invaluable in assessing the occurrence of HPV infection. In addition, there are comments that are debatable, such as the statement by Duane Townsend that cryosurgery is currently the most popular method of treating benign and malignant HPV lesions of the uterine cervix. I wonder if this is the case in the United Kingdom of Europe. In addition, the claim is made that cryosurgery results in cure rates exceeding 90% for most areas of the female genital tract

However, such criticisms are minor compared to the overall excellence of this book. To all those interested in the subject of the human papillomavirus from the gynaecologist to the general practitioner faced with a concerned patient whose recent cervical smear has suggested warty change, here is a readable, well illustrated and affordable introduction to the topic.

Peter Hirsch

Functional Diagnosis of the Lower Urinary Tract by A. Tanko. Akademiai Kiado, Budapest, 1990. 201 pages with figures and tables, £24.00

This short monograph was published in Hungary and has been translated into English. The author's stated intention was to produce a book on functional examination of the lower urinary tract. There are chapters on uroflowmetry, cystometry, pressure flow measurement, urethral pressure profile, sphincter electromyography, and radiological examination. About a quarter of the book is taken up by reproduction of already published reports on standardization of lower urinary tract function produced by the International Continence Society. In general the chapters consist of a description of an investigation with examples of abnormal results. The chapter contents are uneven. In some there is a description of the evolution of a particular test while others try to relate the test findings to the clinical state of the subject. Description of imaging techniques are confined to radiology. Indications for the performance of a particular test and its place in clinical management are not discussed. There are a number of errors and omissions in the book, for example most gynaecologists will find it difficult to accept that the female urethra is held in place by a combination of 'the cardinal, uterosacral and pubocervical ligaments'. The author is clearly enthusiastic about his subject and has intended the book as an aid to colleagues who are starting to study the assessment of lower urinary function. However, since the book is limited to description a doctor starting in this field would be advised to purchase a book with a wider perspective.

D. Warrell

Endoscopic Laser Surgery (Clinical Practice of Gynecology, Vol 2) edited by Michael S. Baggish. Elsevier, New York, Amsterdam, London, 1990. 233 pages with figures and tables, $32, Dfl 82.50

An exciting and expanding new field is dealt with in this volume. It is salutary to note that none of the contributors is from the UK and virtually none of the text references is to UK researchers. This underlies how much laparoscopic surgery has been ignored by all but a few British gynaecologists. Elsewhere progress has been phenomenal, as this book demonstrates.

Not all the answers are here—there is much to be done yet. With this treatise British gynaecologists can plagiarize all the hard work done by others, but not without remembering the comments made regarding training—not that I agree with the transatlantic approach to this particular problem.

The book's title, and those of the individual chapters, belie the vast amount of valuable and general clinical detail stuffed between the covers. You may never wish for a KTP laser, but read this chapter all the same. The inclusion of a chapter on aquadissection greatly enhances the overall appeal. Strangely, the excellent discourse on safety, both as regards lasers as well as laparoscopy, is relegated to the end. There is advice here for anyone who has pretensions with the laparoscope.

The authors, although enthusiasts, refrain from being too overeager to espouse their individual causes. The benefits and disadvantages of specific lasers are described dispassionately.

Consequently, the uncertainty that has been created in the mind of many UK gynaecologists by laser manufacturers is shown to be largely irrelevant. This book is an invaluable guide to making the correct decision regarding the purchase of a laser.

The science is occasionally woolly and unclear. The claims for endoscopic surgery are exaggerated at times, but some of the authors do suggest caution and admit that not all the presumed advantages have yet been proved. The lay out, choice of illustrations and tables are unimaginative, but this should not deter interested colleagues from buying this book or at the very least insisting that it be purchased for the departmental library.

J. A. Davis

Books received some of which may be reviewed at a later date

The Embryo. Normal and Abnormal Development and Growth edited by Michael Chapman, Gedis Grudzinskas & Tim Chard. Springer-Verlag, London, Heidelberg, 1991, 263 pages with figures and tables, £60.00

Sexually Transmitted Diseases. A Textbook of Genitourinary Medicine edited by G. W. Csonka & J. K. Oates. Baillière Tindall, London, 1991, 564 pages fully illustrated, £49.50

Nutrition and Metabolism in Pregnancy. Mother and Fetus by Pēdro Rosso. Oxford University Press, Oxford, 1990, 324 pages with figures and tables, £45.00

Exercise in Pregnancy second edition, edited by Raul Artal Mittelmark. Robert A. Wiswell & Barbara L. Drinkwater. Williams & Wilkins, Baltimore, 1991, 332 pages with figures and tables, £43.00

Birth Without Doctors edited by Jacqueline Vincent-Priya. Earthscan Publications Ltd, London, 1991, 224 pages illustrated, £7.95

Medical Disorders During Pregnancy edited by William M. Barron & Marshall D. Lindheimer. A Year Book Medical Publishers imprint of Mosby-Year Book Inc, 1991, 647 pages with figures and tables

Hysterosalpingography A Text and Atlas edited by David J. Ott & Jamil A. Fayez. Urban & Schwarzenberg, Baltimore, Munich, 1991, 130 pages with figures, £43.00

Transvaginal Ultrasound edited by Melvin G. Dodson. Churchill Livingstone, London, 1991, est. 328 pages, 308 illustrations, £45.00

Handbook of Family Planning edited by Nancy Loudon, foreword by David T. Baird. Churchill Livingstone, Edinburgh, 1991, 484 pages, 59 illustrations, £22.50

Common Obstetric Emergencies edited by Donald M. F. Gibb. Butterworth-Heineman, Oxford, 1991, 128 pages, £10.95

Birth Defects Encyclopedia editor-in-chief Mary Louise Buyse. Birth Defects Encyclopedia is a service of the Centre for Birth Defects Information Services Inc published in association with Blackwell Scientific Publications, Oxford, 1990, 1892 pages, £150.00

Year Book of Neonatal and Perinatal Medicine 1990 edited by Marshall H. Klaus & Avroy A. Fanaroff. Mosby Year Book, St Louis, 342 pages

Erratum

We apologize to G. J. Jarvis author of **Female Urinary Incontinence (Proceedings of an Educational Course held at the Royal College of Obstetricians and Gynaecologists, June 1989)** for misprinting the initial of his name in the review of the book published in the March issue of BJOG.

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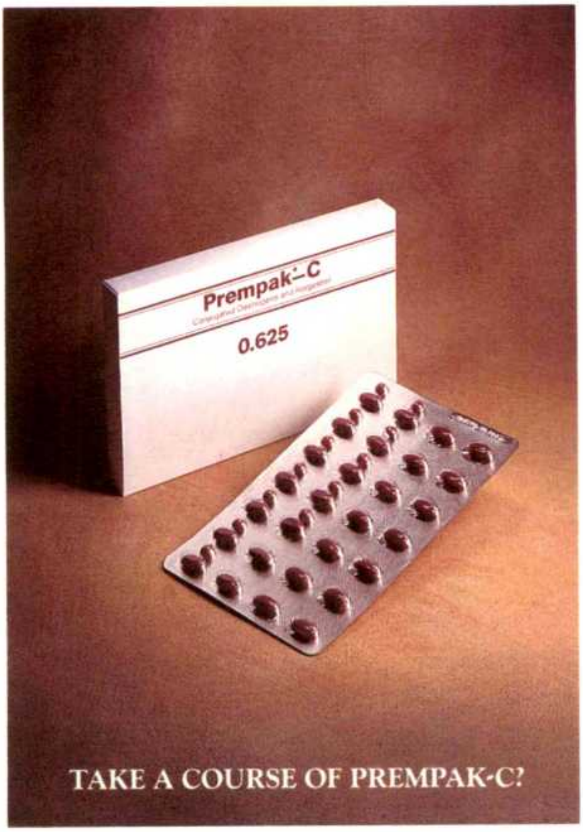

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June 1991, Vol. 98, pp. 509–512

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COMMENTARY

Immunoprophylaxis for rhesus disease—expensive but worth it?

In little over half a century obstetricians have progressed from being perplexed by a disease of unknown aetiology to a useful understanding of rhesus(D) alloimmunization. Screening, investigation and management have been refined but anti-D prophylaxis remains the major effector in prevention. Post-natal and 'sensitizing event' prophylaxis should be an aim of health care systems in developing countries where rhesus disease is perceived as a significant problem.

Haemolytic disease of the newborn (HDN) is caused by antibodies resulting from maternal sensitization following two feto-maternal haemorrhages (F-MH) when the fetus is rhesus positive and the mother rhesus negative. Antibody production following initial sensitization is usually slow and modest whereas a second sensitizing stimulus can lead to very high anti-D levels. The volume of F-MH required to provoke the sensitization is much smaller than that causing initial sensibilization and secondary sensitization occurs most frequently at delivery (MacKenzie *et al.* 1991). Fortunately, immunoprophylaxis is possible by providing the mother with enough exogenous anti-D to remove all the Rh negative cells resulting from an 'average' F-MH.

The protective effect of the administration to the mother of anti-D was demonstrated by Clarke *et al.* (1963). This has become widely adopted in the UK and the incidence of rhesus (D) allo-immunization consequently decreased. Unfortunately the incidence of rhesus(D) sensitization has remained relatively constant since 1973 and the proportion of women sensitized because of inadequate (or omitted) prophylaxis, or unprovoked sensitizing events, has steadily risen, (Eklund 1978; Tovey & Taverner 1981; Tovey 1988).

Without immunoprophylaxis about 1% of Rh(D)-negative women produce antibody by the end of their first pregnancy and a further 3–5% have detectable antibodies 6 months after delivery. Roughly as many women again produce anti-D during a second D-positive pregnancy suggesting that they might have been primarily immunized at their first delivery (Mollison *et al.* 1987). Almost 90% of the sensitizations that follow delivery can be prevented by the administration of anti-D at delivery. Nevertheless, a residual level of (D) sensitization occurs and up to 2% of rhesus(D)-negative women show evidence of antibody production despite prophylaxis (Bowell *et al.* 1985). In addition to post-partum prophylaxis, antenatal administration of anti-D (500 iu anti-D at 28 and 34 weeks) would prevent immunization for virtually all non-sensitized rhesus(D)-negative women (Mollison *et al.* 1987). However, this would require a four-fold increase in hyperimmune anti-D production.

The perinatal mortality rate due to rhesus(D) allo-immunization was 15 per 10 000 births before the introduction of Rh(D) prophylaxis when it accounted for 4·3% of all perinatal losses (Butler & Bonham 1963). By 1983 the incidence of death from this cause had fallen to 0·54 per 10 000 and accounted for 0·3% of perinatal losses (Whitfield 1983). Unfortunately this figure underestimates the true situation as termination of pregnancy for severe rhesus disease (which amounted to twice the number of registered deaths from rhesus disease in 1984 and 1985) and spontaneous fetal losses before 28 weeks gestation were not included (Bowell *et al.* 1985).

Anti-D is produced in the regional transfusion centres by boosting sensitized men and women, extracting the human anti-D by plasmapheresis and sending their gross extraction for centralized pooling, quality control, packaging and distribution by the Bio-Products Laboratory (BPL), Elstree or the Plasma Fractionation Centre (PFC), Edinburgh. Ampoules of anti-D are then returned to the regional transfusion centres for dispensing on prescription by qualified staff. Only two of the eight regions use less anti-D than they produce and they 'subsidize' the other regions in this respect. Current production of anti-D cannot supply enough immunoglobulin to provide ante- and post-natal prophylaxis for every rhesus(D) negative woman in the country and two possible solutions to this problem are being explored: (i) increasing the supply with monoclonal anti-D production and (ii) reducing consumption by lowering the dose of anti-D given. In addition, human anti-D production is fraught with hypothetical and real complications related to the possibility of the injection of blood used to 'boost' the donors being infected (hepatitis, HIV) and supplying contaminated or infected anti-D (not yet recorded). Comprehensive precautions governing the boosting and collection of anti-D designed to prevent the inadvertent contamination of anti-D (and other blood products) are set down in a Department of Health publication (DoH, 1989). These include the exclusion of 'high risk personnel', donor viral and antibody testing, quarantining frozen donor red cells, recipient testing and accurate information on the origin and destination of every BPL product in case contamination is thought to occur. Anti-D is not currently available from the commercial sector. An alternative and unlimited supply of anti-D is promised by workers in the monoclonal antibody field. This technique could produce a standardized product. Stable cell lines producing human monoclonal anti-D have been derived from Epstein-Barr virus (EBV)-transformed lymphocytes (Goosens *et al.* 1987; Kumpel *et al.* 1989) or from heterohybridomas obtained by fusing transformed lymphocytes with mouse myelomas (Thompson *et al.* 1986). More than 50 different IgGs and IgMs have been produced and trials are in progress to confirm their *in vitro* and then *in vivo* suitability for human immunoprophylaxis (Thomsen *et al.* 1990).

The paper by Joseph (1991) in the April issue of this journal raises several general and specific issues related to women's health care provision. He shows that, theoretically, in India prophylaxis would be less expensive than the investigation of affected pregnancies and the treatment of babies with Rh haemolytic disease. In practice, however, the institution of a programme of prophylaxis would mean diverting resources from other health care problems. Such diversion is not practicable and it may be that greater value for money, in terms of disease averted or treated, may be achieved by other savings in the direct uses of personnel and funds.

He argues convincingly that the risk of rhesus disease in India is closely related to number of pregnancies a potential sensitisee has and is therefore beyond the control of the health services (the risk increasing with each additional child). Furthermore the costs of long term community support for handicapped children born from affected pregnancies, are not taken into consideration as they would be in the developed world. A prophylaxis programme is calculated to be beyond the reach of the Indian health care budget. Policies leading to a reduction in family size may be a feasible option in the Indian subcontinent but are not appropriate in the UK where the average number of children per couple is now close to two. Changes in the patterns of disease have occurred as the result of changes in social or economic policy but the reverse situation, where government exhorts a change in social behaviour to effect a major change in health, are less effective and possibly counter-productive.

For example, a reduction in smoking, once its association with lung cancer had been established, had a significant impact on disease patterns in specific groups but, conversely, despite a sophisticated and expensive, multi-media anti-AIDS programme there appears to have been little change in sexual behaviour or awareness of the risks associated with it.

Decision analysis is only one of a variety of economic yardsticks available for appraisal of clinical situations. In decision analysis a probability flow chart is constructed in which the likelihood of a final outcome is the sum of the probabilities incurred at each decision node passed through to reach that point.

Accurate data are vital for its correct construction. Decision analysis has been applied to the economics of antenatal rhesus prophylaxis in the USA by Adams *et al.* (1984) who suggested that a single dose of anti-D at 28 weeks gestation was economically unjustifiable. More recently Baskett & Parsons (1990), using cost-benefit analysis, calculated that it cost 2·7 times less to prevent HDN in one baby than to treat it and pointed out that a large proportion of the extra cost was due to the price of neonatal intensive care. Cost-benefit analysis attaches fixed costs to the factors which need to be taken into account in making certain economic decisions and differs from decision analysis in that it includes issues such as 'quality of life'. There appear to be few areas in our speciality where enough hard data exist to apply either method appropriately. We do not know enough about disease incidence, critical events causing such a disease, diagnostic efficiency, compliance, outcome after different management strategies or the costs of interventions. However, if the objective of such analyses is to generate approximate estimates of costs for different programmes, then rough calculations at the extreme ends of the relevant spectrum are likely to predict whether one of the available options will be financially viable. (An exponential decline between cost and benefit can often be uncovered, as in results of shortening the interval between cervical smears in the cervical cancer screening programme.) If both the 'worst case' and the 'best case' costs are above any available budget then an alternative and completely different solution may be necessary. As we become increasingly aware of the economic constraints on our clinical practice it is vital that when allocated a fixed sum for the management of a specific problem we do not select an option that exceeds that sum and then have to ration the service using historical, geographical, social or political factors, or have to choose a policy that is cheaper but ineffective. Reliable costings require accurate data but do not guarantee practical solutions.

The prospect of monoclonal immunoglobulin technology being able to supply limitless anti-D is alluring but it is a long path from the idea to the application. Following the production of new immunoglobulins there are three stages in selecting suitable types for clinical trials: (i) demonstration of in vitro interaction between D-positive cells and monocytes mediated by the anti-D; (ii) demonstrable antibody mediated red cell destruction in vivo; (iiia) demonstration of suppression of endogenous anti-D production, and (iiib) proving its consequent clinical benefits. Preliminary clinical trials at stage (iiia) of this series are being carried out. It should be remembered that the clinical trials examining the optimum dose, timing and frequency for the administration of pooled human anti-D are still in progress or about to start and their size, complexity and duration are formidable. Similar trials will have to be conducted on monoclonal anti-D before it is introduced for regular clinical use.

Trials examining the effects of different prophylaxis regimens must use either the number of newly sensitized women (disease incidence), perinatal mortality rate or maternal/neonatal morbidity data as measures of outcome. The incidence of rhesus disease can be measured easily but only 5–10% of these women will have antibody levels high enough to significantly affect a subsequent pregnancy and clinical relevance must be considered in association with statistical significance. In rhesus disease the perinatal mortality rate is already so low (<0·5%) that enormous numbers of pregnancies would have to be included in any trial designed to demonstrate a convincing change in fetal/neonatal losses. Maternal/fetal/neonatal morbidity data are necessarily soft, liable to influence by local obstetric and neonatal policy and are subject to a great number of other factors. It would be an enormous task to conduct ideal clinical trials on monoclonal anti-D using perinatal mortality as an outcome measure, tens of thousands of cases and controls would have to be treated to demonstrate a significant benefit at the 5% level. In addition, who would deny a primigravid woman the option of receiving the 'standard treatment' when it is known to be effective? One approach might be to continue primigravid sensitizing event and postnatal prophylaxis with pooled human anti-D and offer 'multips' antenatal prophylaxis with the new monoclonal anti-D and measure the number of new sensitizations as the indication of effectiveness. This could obviate the size limitations outlined above and might avoid some of the ethical conflicts but would yield data of limited clinical significance.

In the developed and developing world it can be shown that postnatal (and possibly antenatal) anti-D prophylaxis is cost effective. Obstetricians are left with the problem of securing an adequate supply of anti-D. Monoclonal production is likely to solve this in the near future but clinical trials will take some time to yield evidence supporting its deployment.

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Management of the pregnant woman with spinal cord injuries

S. J. HUGHES, D. J. SHORT, M. McD. USHERWOOD, H. TEBBUTT

Summary. This paper forms part of an ongoing prospective study of pregnancy and labour in women with spinal cord injuries and combines a prospective and retrospective analysis of 17 pregnancies in 15 women with spinal injuries. The management and outcome in those 17 pregnancies is reviewed.

The purpose of this paper is to review the pregnancy characteristics and outcomes of 17 pregnancies in 15 women with spinal cord injury. These deliveries took place between June 1978 and January 1989 at Stoke Mandeville Hospital and its affiliated obstetric unit at the Royal Buckinghamshire Hospital. Six of the deliveries took place between June 1988 and January 1989 and were observed prospectively, the others were reviewed retrospectively. The spinal injury predated the pregnancy in all the women. The details of the pregnancies are outlined in Tables 1 and 2 and particular reference is made to the associated, potentially serious, complication of autonomic dysreflexia.

The effects of spinal injury

Spinal cord injury causes modifications to normal physiology due to the altered supraspinal influences and spinal reflexes. When the level of the lesion is above T5, voluntary use of the abdominal muscles will be absent. This may impair reflex cough ability thus increasing the potential for respiratory complications. In pregnant tetraplegic women abdominal distension may further compromise essential ventilatory diaphragmatic function.

When the cord lesion is below T12, uterine sensation is said to be intact and contractions are felt normally. These direct sensory pathways will be interrupted with cord lesions above T10. Contractions in women with lesions above T10 may be felt as poorly characterized abdominal discomfort or as an autonomic disturbance caused by reflex responses in the spinal cord below the lesion (Wanner *et al.* 1987). This disturbance may manifest itself in two ways, either (i) a somatic motor output, causing muscle spasms, or (ii) autonomic dysreflexia.

Muscle spasms

These may either be localized to the segments of sensory input or may involve a more generalized response with increased tone and spasms of the abdominal and leg muscles.

Autonomic dysreflexia

This occurs mainly with lesions above T7 and is a response to noxious sensory inputs arising from skin, bladder, bowel and other pelvic organs where the supraspinal influence over the major part of the sympathetic outflow (i.e., T1-L2) has been lost (Linden *et al.* 1980; Mathias & Frankel, 1988). The clinical picture comprises various features reflecting autonomic dysfunction. These commonly include a severe pounding

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Table 1. Clinical characteristics of 17 pregnancies in 15 women with spinal cord injuries. Spinal details*

Pregnancy no.	Age (years)	Spinal lesion level	Bladder evacuation	Known dysreflexia	Parity	Booking gestation (weeks)	Booking urine	Antenatal admissions (excluding elective)
1†	31	T11	Exp	No	G_3P_1	12	Clear	1
2	22	T5	Exp	Yes	G_1P_0	21	UTI	1
3†	25	T5	Exp	Yes	G_2P_1	20	UTI	3
4†	33	T4	S/C	No	G_2P_1	12	Clear	—
5†	24	T10	S/C	Yes	G_2P_0	10	Clear	—
6†	26	T6	S/C	No	G_1P_0	7	Clear	—
7†	25	T4	S/C	No	G_2P_0	35	UTI	—
8	28	T4	Spont.	No	G_1P_0	11	Clear	4
9	39	T5	Exp.	No	G_1P_0	12	Clear	—
10	29	L2	Spont.	No	G_1P_0	27	Clear	1
11	19	T12	Spont.	No	G_2P_1	16	Clear	3
12	27	T12	Spont.	No	G_1P_0	26	UTI	1
13	31	L3	Exp.	No	G_2P_1	18	Clear	—
14	29	T12	Exp.	No	G_1P_0	14	Clear	—
15	34	T7	Exp.	No	G_2P_0	14	UTI	—
16	24	T5	I/C	Yes	G_1P_0	16	UTI	—
17	29	T5	I/C	Yes	G_2P_1	18	Clear	—

* Two women had two pregnancies each; nos. 2 and 3 in one and nos. 16 and 17 in the other.

† Six pregnancies observed prospectively.

Abbreviations: UTI = urinary tract infection; PTL = Preterm labour; S/C = self catheter; Exp. = expression; I/C = indwelling catheter; Spont. = spontaneous voiding; SROM = spontaneous rupture of membranes.

headache, sweating, blotching of the skin and pilo-erection above the level of the lesion. Other symptoms include nasal obstruction, nausea, chest pain, respiratory distress, tremor and anxiety feelings (Linden *et al.* 1980). Hypertension is usually present to a variable degree.

Transient neurological signs and symptoms may also occur as a result of the cerebrovascular effects of hypertension. Lower limb splanchnic vaso-constriction associated with the lack of baro-receptor compensation is also strongly implicated in the sustained hypertensive response (Wallin 1988). Potentially serious complications may result, including convulsions, permanent neurological deficits, intracerebral haemorrhage and death (McGregor & Meeuwsen 1985).

Dramatic changes in blood pressure can occur within seconds of the stimulus accompanied by tachycardia and/or bradycardia (Guttmann & Frankel, 1965; Frankel & Mathias, 1979). During labour, the blood pressure can be observed to rise rapidly with the onset of a contraction and to settle quickly with its cessation. The severity of other symptoms, particularly headache and sweating, parallel blood pressure changes. Dysreflexia must be distinguished from pre-eclampsia, which has many of the same features (Comarr 1965).

Management of autonomic dysreflexia

This involves both identifying and treating its cause and controlling the hypertension (Linden *et al.* 1980). The overdistended bladder in labour and antenatal urinary tract infections are notorious culprits as causes of dysreflexia. Initial anti-hypertensive measures include elevating the head of the bed and prescribing sublingual nifedipine or glyceryl trinitrate. Glyceryl trinitrate skin patches can provide more prolonged vasodilation but some situations require parenterally administered drugs such as intramuscular phentolamine or intravenous labetolol, hydralazine or diazoxide in incremental doses.

The most effective measure for controlling the hypertension is to interrupt the afferent inputs to the spinal cord that are triggering such responses. In patients particularly at risk for autonomic dysreflexia elective use of epidural analgesia will achieve this end.

The management of the above problems

Table 2. Clinical characteristics of 17 pregnancies in 15 women with spinal cord injuries Obstetric details*

Pregnancy no.	Antenatal problems	Gestation at delivery (weeks)	Diagnosis	Dysreflexia		Analgesia	Delivery
				1st Stage	2nd Stage		
1†	Unstable lie 36/52 Anaemia	39	Induction Breech	–	–	Entonox	NVD
2	Ante-partum haemorrhage 34/52	35	APH/ Dysreflexia	+++	+	Epidural	Mid forceps
3†	Anaemia Pyelonephritis ?ROM 33/52 Threatened PTL 34/52 Recurrent UTI	37	Induction ? dates	+++	+ post delivery	Epidural, GTN, Nifedipine, local anaesthetic for suturing	NVD
4†	Recurrent UTI	37	Dysreflexia	++	+++	Nifedipine GTN, Local anaesthetic	NVD
5†	Recurrent UTI Anaemia	37	Dysreflexia	+	+	Pudendal block, local anaesthetic	Keillands rotation & delivery
6†	Recurrent UTI Anaemia	40	Induced	–	–	Elective Epidural	Mid forceps
7†	UTI	37	'Incontinence' head on view	–	+	–	NVD
8	Anaemia Recurrent UTI Recurrent threatened PTL	37	Induced 'poor' CTG	–	+	Entonox	NVD
9	UTI	40	Induced for recurrent spurious labour	+	+	Entonox	Low forceps
10	Recurrent UTI	39	Elective section inlet 10 cm high head poly-hydramnios	–	–	General anaesthetic	C/S
11	Recurrent UTI pressure scores Anaemia	40	Dysreflexia	+	–	Nil	NVD
12	Spurious labour recurrent UTI	38	Tightenings felt. Planned C/S inlet 9·5 cm	–	–	General anaesthetic	C/S
13	–	38	Planned repeat C/S	–	–	General anaesthetic	C/S
14	UTI	40	Tightening felt Dysreflexia	+	+	Nil	Low forceps
15	–	38	Planned C/S. Pelvic deformity	+	++	Nil	Precipitate NVD in spinal unit
16	Recurrent UTI Threatened PTL	31	SROM	–	+	Nil	NVD (5 min after arrival) 1 h after SROM
17	Anaemia & UTI	36	SROM	+	+++	Nil	Low forceps

For abbreviations see Table 1.

forms only part of the overall care of the woman with spinal injuries (Greenspoon & Paul 1986). Close attention is required to bladder and bowel regimens and to skin pressure relief The skin is made more vulnerable by vasoconstrictive responses in the lower limbs even in those not overtly dysreflexic.

Antenatal care and problems

Most of the women listed in Tables 1 and 2 were managed by Stoke Mandeville Hospital (SMH) for their original spinal injury. During their subsequent pregnancies they received shared antenatal care from their local district general hospitals and SMH. They attended SMH on between 2 and 6 occasions before eventual admission. The preferred first visit was in the early second trimester which allowed for baseline investigations and confirmation of delivery dates. Common antenatal events included urinary tract infections, anaemia and elective hospital admissions. Other problems such as antepartum haemorrhage or preterm labour, were not common except when the latter was associated with a urinary tract infection.

Urinary tract infection

This was a significant feature of these pregnancies. Voiding in these 17 pregnancies was by suprapubic pressure in seven, spontaneous in four, by clean intermittent self catheterization in four and two involved permanent indwelling catheters. Advancing pregnancy created problems with incontinence of urine and difficulty with self catheterization. Urinary incontinence may be confused with rupture of the amniotic membranes and vice versa. In pregnancy no. 7 labour was not diagnosed until the fetal head was crowning, a chance finding as a urethral catheter was about to be inserted for incontinence.

Urinary tract infection occurred at some point during pregnancy in all except one woman. Six had asymptomatic infections at booking. Four admissions were precipitated by urinary tract infections and two of these were further complicated by threatened preterm labour. One of these women had marked dysreflexia associated with pyelonephritis. Urine should be cultured at each antenatal visit and consideration given to prophylactic antibiotics if infection persists or recurs. (Comarr 1965).

Anaemia

This represented a minor problem in this group of women. The haemoglobin concentration was <11 g/dl in eight of the pregnancies at some point and in four of these it was <11 g/dl at booking. Haemoglobin concentrations were never below 9·5 g/dl and the use of haematinic agents was often not recorded. Iron should be used cautiously because of the compounding effect of constipation and difficulty with bowel evacuation (Robertson & Guttmann 1963; Rossier *et al.* 1969). Transfusion is the recommended treatment for anaemia in the pregnant woman with a spinal injury (Robertson & Guttmann 1963). This was not required in this series.

Elective hospital admission

This has been advised and reported in published series but a policy of regular vaginal examinations and admission at 32 weeks is no longer practised (Rossier *et al.* 1969). Preterm labour (before 37 weeks) occurred in the present series only when associated with antepartum haemorrhage, urinary infections or a past history of preterm deliveries. Elective admission between 36 and 37 weeks has been the hospital policy since 1988. Elective admission occurred in only six pregnancies. Ten of the others were already in hospital at 37 weeks for reasons such as unstable lie, hypertension, antepartum haemorrhage and spurious labour. One woman arrived in the labour ward at 31 weeks in second stage and this may have been a consequence of recurrent untreated urinary infections. The real necessity of these early admissions was not always clear from the retrospective case reviews.

Usually, elective admission will prevent unattended deliveries. Stillbirths at home have been recorded (Robertson 1972). Pregnancy no. 7 was delivered less than 12 h after elective admission and the missed diagnosis of membrane rupture almost resulted in an unattended hospital delivery. Admission to a spinal unit at 36–37 weeks gestation provides ideal facilities for independent living before labour. This, however, may be totally disruptive to family life when the woman lives outside the immediate hospital area. Admission is also desirable in order to diagnose and manage autonomic dysreflexia before the development of serious sequelae.

Labour—its diagnosis and outcome

Excluding induction of labour and elective caesarean section, labour tended to be diagnosed by either dysreflexic symptoms or membrane rupture with confirmation by palpation of contractions and vaginal examination. Braxton Hicks contractions with slight urinary incontinence may make this diagnosis more difficult as the woman may not experience dysreflexia until late in the first stage. Only three women reported dysreflexia before conception. Dysreflexic symptoms were quite dramatic in the women observed prospectively in their association with contractions, in the second stage and, in particular, when the fetal head was pressing on the maternal perineum. The end of a contraction and delivery result in rapid resolution of all signs and symptoms of dysreflexia.

Management of the dysreflexia was more intensive in the prospective series. This is likely to reflect inadequate records in the women reviewed retrospectively, rather than absence of the condition. However, it would appear that very little specific treatment was instituted. Dysreflexia was a more common finding where the lesion was above T5-7 or if the condition had occurred previously either in the pregnant or non-pregnant state. Severe dysreflexia was associated with pounding headache and diastolic blood pressure >120 mmHg. If patients are not admitted to a spinal unit, they should be managed in a hospital where consultant anaesthetic services for epidural analgesia are immediately available. The medical and nursing staff should be made aware of the potential problems, their significance and treatment.

In this group of women induction of labour was somewhat liberal and the indications were not always clear. When present, dysreflexia increased towards second stage. Although the urge to bear-down was absent, full dilatation, with the head low in the pelvis, was heralded by an increase in blood pressure, pounding headache and profuse sweating in some patients. Contrary to the opinion expressed by Young *et al.* (1983), standard analgesia should be used for instrumental deliveries and perineal suturing despite the apparent lack of sensation. In several of our patients this minimized the dysreflexic symptoms. Perineal infiltration with lignocaine after suturing in pregnancy no 3 (Table 2) led to resolution of her persistent headache.

Mode of delivery

This was influenced by the usual obstetric factors. Paraplegia is not a contra-indication to vaginal delivery. When the injury occurred before puberty or was associated with pelvic fractures, consideration should be given to a possible need for elective caesarean section because of reduced pelvic diameters (Comarr 1965; Robertson 1972). Four were planned in this group, although one of these patients experienced a precipitate labour and normal vaginal delivery of a 2·67kg infant without complication.

Puerperium

There were no third stage problems or post partum haemorrhages. Ergometrine containing drugs should not be used in the third stage. The puerperium was complicated by perineal or urinary infections in five of the 17 pregnancies. One of the patients had a perineal abscess on day 10 and another had an ischial abscess on day 21. Mild anaemia, poor tissues and lack of sensation may have contributed to these problems. The only other significant complication was a pulmonary embolus on the ninth day in pregnancy no. 7. The woman underwent standard treatment with no further morbidity. The women were kept in hospital after delivery for between 2 and 21 days. Retrospective data were inadequate in many cases to assess accurately the length of the postpartum stay.

Perinatal outcome

Perinatal outcome was uniformly good. The weights for infants born after 36 weeks gestation were distributed between 2·4kg and 4·0kg with an average of 3·05kg. There were no fetal abnormalities and no acute anoxia problems. There were no stillbirths or neonatal deaths. Eleven of the 17 infants were male but this is unlikely to be significant. This outcome is much better than in a series reported by Robertson & Guttmann (1963) and probably reflects improved obstetric management.

Comment

The management of the pregnant woman with spinal injuries must consider various factors. Autonomic dysreflexia and its potentially fatal sequelae are a problem to many of these women to a variable degree. Other particular risks for these women include urinary tract infections, anaemia, pressure sores and unattended deliveries.

In the women studied, there was no obvious benefit of elective admission until 36 weeks gestation. Those with high cord lesions, above T5-7, require more intensive management and should be admitted to an appropriate institution. Management of these women requires an experienced team approach. It is not appropriate for a district general hospital to care for an occasional spinal patient. It may be appropriate, however, when several such patients are managed each year at that institution. All medical and nursing staff should be aware of the special needs of these patients, particularly the problems of autonomic dysreflexia and urinary tract infection.

The mode and timing of delivery should be in accordance with the usual obstetric indications. Epidural analgesia is ideal for minimizing dysreflexic symptoms when there is not excessive spinal distortion. Mild dysreflexic symptoms can be reduced by the use of both pudendal nerve blocks and perineal infiltration for instrumental deliveries. Antihypertensive drugs and analgesia were used more commonly in the women observed prospectively.

Perinatal outcome was good in this series. There were no stillbirths, perinatal deaths or infants that were obviously handicapped. These pregnancies occurred well after the spinal injury.

A successful pregnancy should be possible in both paraplegic and tetraplegic women if informed antenatal care and experienced management of spinal labours is available. Several tetraplegic women have been delivered recently but are not included in the time period of this report. They will form part of an ongoing prospective study.

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How does the mode of delivery affect the cost of maternity care?

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Summary. In this paper we present estimates of the difference in the cost of hospital care for women having different modes of singleton delivery. The estimates are based on observation of resources used in different procedures, and on data from the North West Thames Region Maternity Information System. For vaginal delivery the average cost is £363, but could fall between £189 and £773, and for caesarean section the average cost is £1123, with a likely range from £837 to £1560. The wide ranges in the costs of the two modes of delivery reflect variation in the length of stay and in the intensity of care required. The average cost for intrapartum care and postnatal stay is estimated to be £451 for all singleton births. Variation in operative delivery rates between hospitals implies differences in the overall cost of care at different maternity units. This partly reflects differences in the needs of the population served by the units, but also differences in clinical practice. It is important for decision makers to consider the balance between the costs and outcomes of different policies of care.

If the recommendations of the NHS White Paper, Working for Patients (Secretaries of State for Health 1989), are to be implemented, health authorities, as purchasers, will need to know how much maternity care will cost for the women resident in their district, and maternity service providers will need to monitor whether the charge they set for their services reflects the resources they provide. To achieve this, much more detailed information will be required about the costs of maternity care than is currently available.

It has been estimated that £700 million was spent on NHS maternity services in the UK in the financial year 1987/8, an average of about £930 per birth (Comptroller and Auditor General 1990). Recently, NHS hospital costs by specialty have been made available to health service managers (Department of Health 1990). These show that the average revenue cost for *any* inpatient consultant episode in obstetrics, which includes hospital stays without delivery, was £406 in England in 1988/9.

Although care is provided from both community and hospital resources throughout pregnancy and during the postnatal period, health service resources are most intensively used at the

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time of delivery (Gray & Steele 1981). More detailed examination of how the costs around the time of delivery are incurred is a first step towards assessing the costs of different types of maternity care. In this paper we present data from our own observations of costs of consultant unit delivery and immediate hospital postnatal care.

Methods

We have measured the difference in the amount and monetary value of NHS hospital resources required for the care of women having different types of delivery. Our cost estimates are based on data from a combination of sources. Length of labour and postnatal stay for women having different types of delivery were calculated using data from the St Mary's Maternity Information System. This included about 36 727 singleton births in 17 hospitals in the North West Thames Health Region in 1988. Data about the amount and cost of resources used in the care of women during and after delivery were derived from two observational studies at the John Radcliffe Maternity Hospital (JRMH) in Oxford (Clark 1989; Mugford *et al.* 1989). In these studies, we assessed the costs of different elements of care as follows. For labour and delivery, we estimated the average number and category of staff present for women having different types of delivery. The staff cost was then estimated from the median length of labour and the type of delivery. To this we added the cost of materials, drugs and running costs of equipment used. For the postnatal stay, we estimated the cost per day, including staff and materials, of ward care for women with different types of delivery, with and without infection. This was multiplied by the median length of stay to arrive at the total cost of postnatal care. The total cost for labour and postnatal care includes an average daily hospital overhead cost. Capital costs are not included.

In this paper we have concentrated on the most frequent types of delivery, and have excluded multiple births. Deliveries by caesarean section have been subdivided by whether they were planned before the onset of labour (elective) or not (emergency), and by whether they were performed before the onset of labour (antepartum) or during labour (intrapartum). The cost of normal care of the newborn baby in the postnatal ward is included, but we have excluded any additional cost of special care for the newborn baby. Throughout, we have estimated average costs, rather than the marginal costs of additional cases. All financial costs are given at 1989 price levels.

Results

Table 1 shows the differences in length of labour and length of postnatal stay for the women in this study. Nearly 12% of deliveries were by caesarean section, and a further 9·6% by forceps or ventouse. Median length of labour was longer for vaginal operative deliveries than for spontaneous deliveries, and in the case of intrapartum caesarean section, longer for emergency sections than for elective sections. Median postnatal stay was longer after caesarean section than after vaginal delivery.

Table 2 shows the estimated cost and range of costs by mode of delivery. For a vaginal delivery the cost is £363, with a 10th–90th centile range from £189 to £773, with higher costs for operative and breech deliveries. A caesarean section cost £1123, with a 10th–90th centile range between £837 and £1560. Costs are higher for emergency than for elective caesarean, and are also higher if the operation is performed after the onset of labour. From these figures, we estimate that the average cost of hospital delivery and postnatal care for women having a singleton birth is £451 at 1989 prices.

The largest part of the cost of care is accounted for by the length of the postnatal stay. The cost of postnatal care after operative delivery is higher than that after spontaneous vaginal delivery because women who have operative deliveries stay longer in hospital and are also more likely to have postnatal complications, such as infection (see Table 1), which require more care.

Although use of resources during labour and delivery is likely to be more intensive than during the postnatal stay, these account for a smaller proportion of the overall cost of care However, labour ward costs also differ by mode of delivery. This reflects the number and qualifications of staff required, and the length of time that a woman is in labour. Thus the cost is highest for women who have been in labour and then require an abdominal delivery.

Discussion

Our findings confirm that, as might be expected,

Table 1. Length of labour and length of postnatal stay by mode of delivery North West Thames Region 1988

Mode of delivery	No. of deliveries	Mention of infection	Time from onset of labour to delivery (h)	Length of postnatal stay (days)
	Number (%)	Number (%)	Median (10th–90th centile)	Median (10th–90th centile)
Vaginal delivery				
Spontaneous	28468 (77·8)	539 (1·8)	6·3 (2·6–12·7)	2 (1–5)
Forceps/ventouse	3507 (9·6)	179 (5·1)	10·7 (5·3–18·3)	4 (2–6)
Breech	399 (1·1)	14 (3·5)	6·8 (2·8–13·9)	3 (1–6)
All vaginal	32374 (88·4)	732 (2·3)		
CS emergency				
Antepartum	578 (1·6)	107 (18·5)	—	7 (5–11)
Intrapartum	2189 (6·0)	417 (19·0)	9·7 (3–18·9)	7 (5–9)
CS elective				
Antepartum	1431 (3·4)	233 (16·3)	—	6 (5–9)
Intrapartum	61 (0·2)	7 (11·4)	4·1 (1·4–10.5)	6 (4–8 8)
All CS	4259 (11·6)	764 (18·0)		

CS = caesarean section.

the hospital costs to the NHS are higher for operative than for spontaneous delivery. As the length of stay data are derived from a large number of births in a range of different hospital settings, we are confident that the range of costs is likely to be representative of most NHS units. The most recent published national data about maternity hospital activity, for 1985, show that operative delivery rates in the North West Thames Region were comparable with other

Table 2. Costs of hospital delivery and postnatal care by mode of delivery in £ sterling at 1989 prices

Mode of delivery	Cost of labour and delivery (£)	Cost of postnatal care (£)	Total cost (£)
Vaginal delivery			
Spontaneous	93 (53–161)	234 (117–585)	327 (170–746)
Forceps/ventouse	164 (102–252)	476 (238–714)	644 (340–966)
Breech delivery	131 (82–217)	354 (118–708)	485 (340–966)
All vaginal delivery	101 (59–172)	262 (130–601)	363 (189–773)
CS emergency			
Antepartum	154 (no labour)	889 (635–1397)	1043 (789–1551)
Intrapartum	283 (206–389)	889 (635–1143)	1172 (841–1532)
CS elective			
Antepartum	154 (no labour)	756 (630–1134)	910 (784–1288)
Intrapartum	218 (188–292)	738 (492–1082)	956 (680–1374)
All CS	281 (206–386)	842 (631–1174)	1123 (837–1560)

CS = caesarean section. The figures in parenthesis show the 10th–90th centile range.

health regions in England and Wales (OPCS 1988). The introduction of new accounting and management systems in the wake of the NHS White Paper may generate data which could confirm or improve on our findings, but there may be difficulties in obtaining information about costs in different centres if recommendations are accepted that cost data should be confidential information (Information Management Group 1990).

We have compared our results with available data about federal rates of reimbursement for maternity care under Medicaid in the United States (Resnick *et al* 1987). The costs calculated for Medicaid reimbursement in 1986 for diagnostic related groups in obstetrics are shown in Table 3. Converted to sterling and current price levels, the costs are much higher than our figures, probably reflecting higher salaries, and a larger element for hospital capital costs (not included in our estimates) and overheads.

The ratio of costs for the different categories differs from the ratio of costs of care by mode of delivery that we observed. This is principally because vaginal delivery without complications is very much less costly in the UK than in the US. This may be for several reasons. Firstly, these are supervised by midwives in the UK but by medical staff in the United States. Secondly, our costs are only for singleton births (about 98% of all births). Costs for a multiple birth have been estimated by one of us, and are likely to be higher (Mugford 1990). Thirdly, although we have not used the ICD-9 classification for mode of delivery used for diagnostic related group calculations, average length of stay for the different diagnostic related groups quoted by Resnick *et al.* (1987) are similar to those for all of our groupings except uncomplicated vaginal delivery, which was associated with a shorter postnatal stay in NW Thames Region than in the USA. Most postnatal care in the UK, but not in the US, for women with uncomplicated deliveries is carried out by community midwives after discharge from hospital, so that total costs of maternity care may be closer between the two countries than is reflected in hospital costs alone.

Variations in the average cost of a consultant episode, shown in the Department of Health (1990) specialty cost data may partly reflect differences in operative delivery and complication rates between units. This in turn will be determined by differences both in the needs of mothers delivered at different units, and by differences in clinical practice.

Our data show clear implications for resource use arising from different forms of care. There are also differences of opinion amongst clinicians about appropriate levels of intervention (Rockenschaub 1990). Because resources are always limited, clinicians and managers know that there are 'opportunity costs' that arise from their decisions. The opportunity cost of using the resources in one way is the benefit foregone because they are denied for another use. If it can be shown that they would achieve greater benefit in that other use, then resources are being used inefficiently.

There is now a considerable body of evidence to indicate that different approaches to care during pregnancy and childbirth may influence the mode of delivery as well as the subsequent outcome for mother and baby (Chalmers *et al.* 1989). An increased rate of operative delivery

Table 3. Comparison of data from US and UK about costs of hospital care for childbirth

	US federal reimbursement rates (Medicaid)			Estimated costs for UK maternity unit	
Mode of delivery	US $ 1986	£ sterling 1989*	Ratio to cost of uncomplicated VD	£ sterling 1989	Ratio to cost of uncomplicated VD
Vaginal delivery (VD)					
Without complications	1219	978	1·00	322	1·00
With complications	1660	1332	1·36	660	2·05
Caesarean section					
Without complications	2261	1814	1·85	966	3·00
With complications	2933	2357	2·41	1167	3·62

US data taken from Resnik *et al.* (1987).

*£1 = $1.4672 in 1986 (average), UK consumer prices increased by 17·8% from 1986 to 1989 (Financial Statistics, HMSO).

may be justified if there is an associated improvement in outcome, including both mortality and short and long term morbidity. However, we can give examples which illustrate how certain forms of care may lead to inefficient use of resources. Firstly, the widespread use of continuous electronic fetal monitoring in labour to detect fetal distress *without* use of fetal blood sampling to confirm a suspected diagnosis of fetal asphyxia increases caesarean section rates, but there is no evidence that continuous monitoring is superior to intermittent auscultation in terms of outcomes for either babies or mothers (Grant 1989). Our data suggest that the additional resources required as a result of this excess of abdominal deliveries might be considerable, and could be put to better use. There is also scope for reducing the post-operative infection rates, and hence the cost of hospital care, for women who have had caesarean sections (Mugford *et al.* 1989). Furthermore, there is accumulating evidence that the progress of labour and delivery is dependent on the form of care and support received by women in labour (Keirse *et al.* 1989). It is often supposed that the cost of a constant companion in labour would increase the cost of maternity care, especially if it requires a qualified midwife for each woman in labour. However, if such a policy resulted in lower operative delivery rates and reduced need for pain relief, additional costs of midwifery staff could at least partly be offset by the reduced costs of care resulting from these changes.

As district health authorities assess and plan for their residents' need for maternity care, and as 'provider' units estimate the costs to them of meeting these needs, both will have become aware of the pressure to optimize the benefit to be gained from limited resources. Following these changes in the NHS, there is concern that decisions will be made on the basis of cost alone, with insufficient consideration of quality of care and outcomes. The data we have presented offer one step towards understanding the *cost* consequences of different policies of maternity care. It is important for decision makers to balance costs with outcomes. Whether there is scope for changing these policies is a matter which managers and clinicians will have to decide in the contexts of clinical audit and resource management.

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Head circumference/abdominal circumference ratio, ponderal index and fetal malnutrition. Should head circumference/abdominal circumference ratio be abandoned?

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Summary. Head circumference/abdominal circumference (HC/AC) ratios of the fetus are accepted as a means of distinguishing different patterns of growth retardation with a high ratio implying malnutrition of the fetus. Ponderal index (birthweight/length^3) is used by paediatricians as a measure of neonatal wasting and would therefore be expected to correlate with HC/AC ratios at delivery. Anthropometric data on 999 newborn infants have been collected and analyzed by multiple regression. The results show a poor correlation between ponderal index and HC/AC ratio, worse than that between ponderal index and AC alone. The use of HC/AC ratios antenatally to identify subgroups of intrauterine malnutrition should be abandoned. The prediction of intrauterine malnutrition by weight/length ratios should be investigated further.

The concept of intrauterine growth retardation (IUGR) as defined by low birthweight for gestational age is now outdated since a proportion of malnourished infants will in fact have a birthweight >10th centile (Altman & Hytten 1989).

Birthweight is not a valid measure of fetal growth impairment and to facilitate diagnosis of intrauterine malnutrition it is necessary to incorporate body length and calculate the ponderal index (birthweight/length^3) corrected for gestational age (Miller & Hassenein 1971).

Malnourished infants have a low ponderal index irrespective of their position on birthweight-for-gestational age charts. It has been clearly demonstrated by many authors that a low ponderal index significantly correlates with asphyxia, acidosis, poor neonatal outcome and neurological dysfunction later in life (Walther & Ramaekers 1982; Patterson & Pouliot 1987). Traditionally IUGR has been categorized as symmetrical or asymmetrical, identified by the ratio of fetal head circumference (HC) to abdominal circumference (AC) measured by ultrasound (Campbell & Thoms 1977). An increased HC/AC ratio appears to represent a fetal adaptation to uteroplacental insufficiency and suggests preferential redistribution of cardiac output favouring brain development.

Since both HC/AC ratio and ponderal index

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purport to detect malnourished babies, there should be a substantial correlation between these two measurements. Recent anecdotal observations have challenged this correlation and the aim of the study was to investigate whether any such correlation exists.

Subjects and methods

The study included 1000 infants born at University College Hospital, London in 1987/88 over a 6-month period and informed consent was obtained from the mothers. One author (J.T.) made all the measurements. No baby less than 32 weeks gestational age was included in the study The group of infants was a target size but the births were not consecutive since measurements were only taken during the working week of one author (J.T.). The data collected on each baby included the mother's parity, ethnic origin, the sex of the baby, the period of gestation calculated from the last menstrual period unless an early ultrasound showed a discrepancy of more than 10 days (in which case the ultrasound dates were used), the birthweight, the crown heel length, head circumference and abdominal circumference of the baby. The last three measurements were all made between 24 and 48 h of age to exclude inaccuracies due to moulding of the head during delivery. A tape measure was used to measure the maximum occipito frontal circumference above the level of the ears and abdominal circumference was measured immediately above the umbilical cord. Measurements were made in centimetres and were made with the baby in a quiet state i.e., not crying.

Crown heel length was measured by placing the baby in a shallow box with a moveable footboard so that its left side was against the left side of the box with the head on the examiner's left touching the centre of the fixed end of the box. To obtain the tonic neck reflex the infant's head was rotated to the right by the examiner's left hand while the right hand extended fully the right leg. The footboard was brought up so that it touched the sole of the foot in its entire length. The crown heel length was read off directly from a centimetre scale on the side of the box to the nearest 0·5 cm.

Before the study J.T. made ten measurements of head circumference, abdominal circumference and crown heel length on five babies to establish the reproducibility of the measurements. An unmarked tape was used and actual measurements were recorded by G.H. The coefficients of variation for reproducibility were 0·53% for head circumference, 1·62% for abdominal circumference and 0·75% for length.

One baby in the study was measured twice in error and so data were collected from 999 babies.

Statistical methods

The statistical analysis was done using multiple regression, with the anthropometry analyzed as natural logarithms, and log ponderal index (PI) as the dependent variable. The log transformation was necessary (a) to compensate for skewness in the PI distribution, (b) to make more similar the standard deviations of PI at different gestational ages, and (c) to allow for generalized indices of the form $HC.AC^p$, of which HC/AC ratio is a special case, to be included in the regression. This latter point is explained as follows: consider the multiple regression equation

$$\log PI = k + q \log HC + r \log AC, \qquad (1)$$

where q is the regression coefficient of log HC, r is the regression coefficient of log AC and k is the intercept. This equation can be rearranged as

$$\log PI = k + q \log (HC.AC^p) \qquad (2)$$

where p is equal to the ratio r/q. This shows that $HC.AC^p$ is the optimal index for predicting PI. Now if HC/AC, or equivently $HC.AC^{-1}$, is actually the best index, then p should be close to -1, and the two regression coefficients q and r should be approximately equal and opposite in sign. Fitting equation (1) allows this hypothesis to be tested.

Other confounding variables considered in the analysis were gestational age, parity, multiple pregnancy, ethnic group and the infant's sex. These were represented in the regression by sets of dummy variables, one per level for each variable. Various regression equations were fitted with different combinations of the confounding variables included, to determine which were important in affecting the PI-HC-AC relationship. Initially logPI was regressed on each of log HC, log AC and log HC/AC in turn, and then on log HC and log AC together (equation 1). Regressions of log PI on log birthweight and log length were also looked at. The results show that gestational age was the only confounding variable to affect the relation, and that adjustments for parity, twinning, ethnic group and sex made no difference.

The strength of the relation between PI and each anthropometric variable was measured by the partial correlation. This is calculated as the square root of the fraction of total variation in log PI accounted for by the variable, after adjusting for confounding variables. When no confounding variables are fitted, the partial correlation is the same as the conventional correlation coefficient.

Results

The 999 infants consisted of 500 girls and 499 boys; 525 were born to primiparous women and 474 to multiparous; 974 were singletons, 22 were twins and 3 were triplets; 756 of the babies were white, 110 were Indian/Bangladeshi, 77 were African and the remaining 56 were Malaysian, Arab, South American or Oriental.

Table 1 shows the partial correlations of PI with the other measurements, after adjustment for gestational age. Although all the correlations were highly significant ($P<0{\cdot}001$), PI correlated relatively poorly with HC.AC ratio ($r = 0{\cdot}32$) (Figure 1) and was actually worse than for AC by itself ($r = 0{\cdot}40$). Fitting the regression equation (1) gave values of 0·17 (SE 0·09) for q the HC regression coefficient, and 0·45 (SE 0·05) for r the AC coefficient. Thus the ratio r/q was 2·6, indicating that the optimal HC-AC index was close to HC.AC^3. In addition, since q was insignificantly different from zero ($P>0{\cdot}05$), there was not justification for including HC in the regression equation—AC in itself was just as informative. This is shown in Table 1 by the partial correlation of PI with HC.AC^3 being no greater than for AC alone.

The correlation of PI with birthweight was 0·50, and with length −0·17

Discussion

An increased HC/AC ratio in a fetus that is small for gestational age on ultrasound biometry is usually categorized as asymmetric growth retardation and is supposed to represent late onset wasting of the baby. If this increased ratio truly represents late onset wasting this will also be reflected in a low ponderal index at birth. Similarly a normal HC/AC ratio in a small-for-gestational age (SGA) fetus is usually called symmetrical growth retardation and is thought to mainly represent a constitutionally small infant but may include a group that has suffered from an early intrauterine insult. If this normal HC/AC ratio does represent mainly constitutionally small infants this group will have a normal ponderal index at birth.

Table 1. Correlations with ponderal index (birthweight/length^3)

Birthweight	0·50
Length	−0·17
Head circumference (HC)	0·26
Abdominal circumference (AC)	0·40
HC/AC ratio	0·32
HC.AC^3	0·40

However, in the present study the ponderal index correlated poorly with HC/AC ratio suggesting that the latter cannot be used to diagnose malnourished infants *in utero*. In fetuses that are SGA on ultrasound biometry, the division into 'late onset wasting' and 'constitutionally small' by HC/AC ratio is inappropriate.

Previous workers have concentrated on babies who are SGA as they are known to have a high perinatal morbidity and mortality. However, by definition a large proportion of healthy babies will be included in this population. These are the fetuses who are constitutionally small but have reached their full growth potential.

Obstetricians' previous obsession with birthweight fails to detect malnourished babies with a birthweight above an accepted normal level whilst at the same time concentrating intensive fetal health assessment techniques on a group mainly consisting of normal but small babies.

The results of this study show that the abdomi-

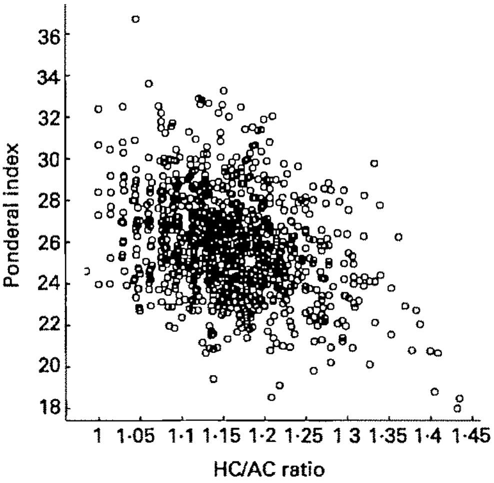

Fig. 1. Correlation between ponderal index and head circumference/abdominal circumference (HC/AC) ratio.

nal circumference is better than HC/AC ratio for predicting ponderal index. However, this only improves the correlation from 0·32 to 0·40 (Table 1), which is far too small a correlation to be useful for prediction purposes. We suggest that rather than using HC/AC indices we should try and identify malnourished infants *in utero* by using a weight/length index. Since there is a relation between femur length and fetal length it is possible to calculate an *in utero* ponderal index (Vintzileos 1986). However, small errors in femur length estimation will result in large errors in ponderal index due to the cubing of the femur length. Other biometric ratios need investigating since both abdominal circumference/femur length and thigh circumference/femur length ratios have been shown to correlate with neonatal ponderal index (Hays & Patterson 1987). Finally future energies must be directed towards the concept of fetal health not birthweight.

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A randomized comparison of oxytocin, sulprostone and placebo in the management of the third stage of labour

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Abstract

Objective—To compare the effect on post partum bloodloss of the postpartum prophylactic administration of oxytocin or sulprostone in low risk women having an expectant management of the third stage.
Design—Randomized, placebo controlled, double-blind trial.
Setting—Radboud University Hospital, Nijmegen (67 women) and Lievensberg Hospital, Bergen op Zoom (10 women).
Participants—77 women entered the trial (three were excluded).
Interventions—The intramuscular injection, immediately after the birth of the baby, of either oxytocin 5 IU, sulprostone 500 μg or 0·9% saline.
Main outcome measures—Quantitative postpartum blood loss and length of third stage.
Results—Postpartum blood loss was reduced almost equally, by about 35%, by oxytocin ($P = 0{\cdot}02$), or sulprostone ($P = 0{\cdot}05$). The mean length of the third stage was shorter in both groups receiving the active treatment, this effect was significant in the sulprostone group ($P = 0.01$).
Conclusion—Prophylactic administration of oxytocin or sulprostone directly after delivery followed by expectant management of the third stage reduces post partum blood loss and shortens the third stage.

Any means of reducing blood loss in the third stage without considerable side-effects is welcomed in labour and postpartum care for the well-being of mother and child. We designed a randomized placebo controlled double blind trial of the effect of prophylactic administration of oxytocin, sulprostone or saline intramuscularly, on post partum blood loss.

Sulprostone, a synthetic prostaglandin $E_2(PGE_2)$ derivative (16-phenoxy-17, 18, 19, 20-tetranor-PG E_2-methyl sulfonamide), was chosen because in animal studies it has been found to have a greater uteroselectivity than 16, 16-dimethyl-PG E_2 and 15 methyl-PG $F_2\alpha$ and less effect on the smooth muscles of the gastero-intestinal tract, blood vessels and bronchi (Hess *et al.* 1979).

Oxytocin was chosen because it is less likely to cause hypertension than ergot alkaloids (Vaughan Williams 1974, Elbourne *et al.* 1988), does not influence prolactin levels (Symes 1984) and is less likely than ergot derivatives to cause headache, nausea and vomiting (Friedman 1957). In the Netherlands an intramuscular injection of 5 IU oxytocin is generally used in the active management of the third stage.

Subjects and methods

The study was performed between April 1986 and April 1988 at the University Hospital in Nij-

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megen (67 women) and the Lievensberg Hospital in Bergen op Zoom (10 women). The inclusion criteria were uncomplicated, singleton, term pregnancies with spontaneous uterine activity and a spontaneous vaginal delivery. Women were excluded if they had a Hobel score of more than 10 (Hobel *et al.* 1973). Women in early active labour were asked to participate in the study and received written information about the trial. The ethics committee of the University Hospital approved the study. If the woman agreed to participate she entered the trial when the injection was given.

Power calculations to determine an appropriate sample size resulted in an initial group size of 50 subjects (lognormal distribution of blood loss, reduction in blood loss for oxytocin and sulprostone with respect to saline at least 30%; coefficient of variation (SD/mean) 100%, power 80%, β error 20%, α error 5%). A treatment allocation list was prepared for 150 women (5 blocks of each 30 women, randomization was within each block so that 10 women received each of the three treatments). Four blocks were recruited at the University Hospital and one block at the Lievensberg Hospital. The trial was stopped after 2 years for organizational reasons.

The hospital pharmacy supplied numbered boxes containing 5 IU oxytocin or 500 μg sulprostone or saline according to the treatment allocation list. Allocation of the boxes was by order of entry of the woman to the labour ward. A nurse not working in the labour room where the delivery was taking place prepared the injection. Directly after the birth of the baby, 5 IU oxytocin (Organon) or 500 μg sulprostone (Schering) or saline was given intramuscularly. The third stage was managed conservatively. The cord was clamped within 1 min of bith. After signs of detachment or descent of the placenta the woman was asked to push. Neither umbilical cord traction nor fundal pressure was used.

Blood loss was calculated by measuring the amount of blood and clots collected in the bedpan and by weighing the bloodstained swabs and linen obtained during 1 h post partum.

Seventy seven women entered the trial. Three were excluded because of induction of labour (in two) and vacuum extraction (in one). In spite of randomization, there were more multiparous women with fewer episiotomies in the sulprostone group than in the other two groups. To adjust for these factors and because of the small number of women within the homogeneous subgroups with regard to treatment, parity and episiotomy, a logarithmic linear regression model (SAS User's Guide 1985) was used for analysis:

$$\ln (V) = \ln (Vo) + \sum_{i=1}^{4} bi^{*} Xi + e$$

X1 = parity (0 = primi, 1 = multi)
X2 = episiotomy (0 = no, 1 = yes)
X3 = oxytocin (0 = no, 1 = yes)
X4 = sulprostone (0 = no, 1 = yes)

In (V) being the natural logarithm of the measured blood loss; Vo representing the median amount of bloodloss if all Xi = 0, and *e* representing the (normal) variation in the logarithm of the blood loss between women in the selected population. This model describes the distribution of the measured blood loss within the homogeneous group of deliveries defined by the above mentioned variables.

The statistical significance of the regression coefficients bi (i = 1, 4) are tested according to the standard multiple regression analysis procedure. If the resultant *P* value is $\leqslant 0{\cdot}05$, the regression coefficient is significantly different from zero. Comparisons between the three groups with regard to the length of the third stage of labour was by standard one-way analysis of variance.

Results

Table 1 shows the distribution by parity and episiotomy in the different treatment groups. Observed blood loss in the sulprostone group was remarkably lower than in the saline group (Table 2). Model estimates of the median bloodloss for different groups of deliveries adjusted for other factors show that multiparous women experience 30% less bloodloss than primiparous

Table 1. Distribution of parity and episiotomy in the three treatment groups

	Oxytocin (*n* = 28)	Sulprostone (*n* = 23)	Saline (*n* = 26)
Primiparous	19 (68%)	7 (30%)	14 (54%)
Episiotomy	17 (61%)	9 (39%)	14 (54%)
Exclusions			
Induced labour	0	1	1
Instrumental delivery	0	0	1

Table 2. Measured blood loss and length of third stage in the three treatment groups

	Oxytocin ($n = 28$)	Sulprostone ($n = 22$)	Saline ($n = 24$)
Measured blood loss (ml)			
Mean (SD)	374 (279)	324 (302)	548 (376)
Median	300	238	402
Range	75–1100	70–1420	70–1500
≥500 ml	7 (25%)	5 (23%)	10 (42%)
≥1000 ml	2 (7%)	1 (5%)	3 (12%)
Additional oxytocics	0	0	2
Length of third stage (min)			
Mean (SD)	9·9 (7·4)	8·1 (7·5)	11·7 (6·4)
Median	7·5	5·0	10·5
Range	3–33	2–34	5–33

($P = 0{\cdot}05$ logarithmic linear regression model), that an episiotomy increases the bloodloss by 30% ($P = 0{\cdot}04$) and that intramuscular injection of 5 IU oxytocin or 500 μg sulprostone reduces the post partum blood loss by almost 35% (oxytocin $P = 0{\cdot}02$, sulprostone $P = 0{\cdot}05$). The mean length of the third stage in the oxytocin group (9·9 min) and in the sulprostone group (8·1) was 20–30% shorter than that in the saline group (11·7 min) this difference was statistically significant ($P = 0{\cdot}01$). Retained placenta did not occur. One woman in the saline group experienced nausea.

Discussion

Baumgarten *et al.* (1983) compared uterine activity in the puerperium after the intramuscular administration of 500 μg sulprostone or 2 IU oxytocin or 0·2 mg methergin or saline. Sulprostone acted most quickly (3·9 min), followed by oxytocin (4·4 min) and methergin (9·7 min). Uterine activity stimulated by methergin lasted 162 min followed by sulprostone 102 min and oxytocin 45 min. Elbourne *et al.* (1988) considered that there was no support for the routine use of ergot alkaloids in the third stage management because there was no evidence that they are more effective than other preparations and they have unwanted pressor effects. Prophylactic administration of oxytocic drugs has been criticised because it could create a cascade of intervention (Inch 1985). Our study showed that the prophylactic administration of oxytocin or sulprostone as the only active management of the third stage reduced post partum blood loss and could shorten the third stage without promoting a cascade of intervention. Due to the small number of women it was not possible to study the effect of these drugs on the occurrence of post partum haemorrhage. These findings agree with those of Prendiville *et al.* (1988) who showed that active management of the third stage reduced the occurrence of post partum haemorrhage and shortened the third stage.

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How obstetricians manage the problem of preterm delivery with special reference to the preterm breech

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Summary. A questionnaire regarding the route of birth for the preterm fetus with particular reference to the management of the preterm breech was sent to 180 consultants in England and Wales. Only 23% of respondents use electronic fetal monitoring below 26 weeks gestation and only 12% use caesarean section routinely for fetal indications at less than 26 weeks. Only 12% will use caesarean section for the preterm fetus presenting by the vertex in uncomplicated labour. Only 35% of all respondents consider that there is sufficient evidence to support the use of caesarean section for the uncomplicated preterm breech, but 76% will actually use caesarean section for this indication. Overall 71% reported that they are affected by medicolegal considerations in their management of the preterm breech. Overall, 83% said that they might change their practice regarding the mode of delivery of the preterm breech in the light of the findings of a randomized prospective controlled trial.

Over the past 20 years the chances of survival of the preterm infant have improved dramatically (General Register Office 1970, Office of Population Censuses and Surveys 1988). As a result abdominal delivery is being used more frequently at gestations where previously the fetus was considered to be too immature to survive (Effer *et al.* 1983; Goldenberg & Nelson 1977; Lamont *et al.* 1983; Rosen & Chik 1984; Westgren *et al.* 1985; Gimovsky & Petrie 1988). For example, numerous retrospective non-randomized studies have suggested that preterm fetuses presenting by the breech have a better outcome when born by caesarean section than when born vaginally and, therefore, abdominal delivery should be routine. The adoption of such policies has been increasing despite knowledge that retrospective data is fundamentally flawed by the inability to exclude bias (Bowes *et al.* 1979) This has led to calls for a proper prospective randomized controlled trial (Lamont 1985; Grant 1986).

In 1988 Birthright funded a pilot study to determine the feasibility of such a trial in the United Kingdom. Part of this study was a postal survey of the opinions of a representative sample of obstetricians to establish current opinion and practice regarding mode of delivery of the preterm infant.

Methods

To obtain a representative sample of obstetricians practising in England and Wales, a multiple choice questionnaire was sent to all 180 consultants in four health regions from the North, Midlands and South of England, and

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Table 1. Questionnaire to establish opinion and practice regarding preterm delivery

(1) What is your age?
(2) In which year did you gain your MRCOG?
(3) What is the lowest gestational age at which you would usually perform intrapartum fetal heart monitoring?
22/23/24/25/26/27/28/29/30/>30 weeks
(4) What is the lowest gestational age at which you would usually perform a caesarean section for fetal indications?
22/23/24/25/26/27/28/29/30/>30 weeks
(5) Would you usually perform a caesarean section for the very preterm fetus (26–32 weeks gestation), presenting by the vertex, in uncomplicated preterm labour in order to protect the fetus?
Yes/No
(6) Do you feel that there is enough scientific data to support the use of caesarean section as the preferred mode of delivery for the very preterm infant in otherwise uncomplicated breech presentation in spontaneous labour?
Yes/No
(7) At which gestational ages would you perform a caesarean section for an uncomplicated breech presentation in spontaneous labour?
22/23/24/25/26/27/28/29/30/>30
(8) Indicate how much the current medicolegal climate influences your obstetric management of the delivery of the preterm infant
Strongly/Moderately/Not at all
(9) If the results of our study (which was described in the introductory letter) on the optimum mode of delivery of the preterm breech infant are at variance with your current practice, would these results change your opinion in the future regarding the management of your own patients?
Yes/No

Wales. This is a sample of 25–30% of all consultants in England and Wales and it was felt that this would provide an adequate reflection of consultant opinion. The names were obtained from the list drawn up by the National Perinatal Epidemiology Unit in 1987. The questions asked are listed in Table 1.

Statistical analysis used the Statistical Package for the Social Sciences (SPSS), PC version.

Results

The response rate was 72% (130 out of 180). Nine consultants had retired or no longer practised obstetrics and their replies were excluded from analysis. Overall 92% of consultants were male; women's responses did not differ significantly from those of their male colleagues. The overall mean age was 49 years; 92% practised at a district general hospital, and 8% at a teaching hospital; 14% had obtained the MRCOG less than 10 years previously (Table 2). Personal characteristics of non-responders (obtained from the RCOG register) were not significantly different to responders except that they had obtained their MRCOG on average 4 years earlier and only 4% were within 10 years of membership (χ^2 6·1, $P<0{\cdot}001$). There was no significant variation in the proportion of non-responders by region.

Figure 1 shows the lowest gestation at which electronic fetal monitoring (EFM) would be used for preterm fetuses in any presentation. There was a marked preference for selecting gestations with an even number of weeks (i.e. 24, 26, 28 weeks, rather than 25, 27, 29), therefore the results have been shown in 2-week epochs. Only 23% of consultants would use EFM before 26 weeks. Similarly, only 12% would perform a section before 26 weeks (Fig. 2). Readiness to perform a caesarean section before 26 weeks was affected by the age of the consultant. No consultant aged over 55 ($n=20$) would do so, compared with 29% aged 46–55 ($n=52$) and 71% aged 36–45 ($n=41$). Not surprisingly, the gestation at which section would be performed was closely linked to the gestation at which EFM would be used ($r=0{\cdot}68$, $P<0{\cdot}00005$).

Table 2. Characteristics of responders and non-responders

	Responders	Non-responders
Male	92%	94%
Female	8%	6%
Teaching hospital	8%	14%
District general hospital	92%	86%
Mean year of obtaining MRCOG	1970	1966
Mean age of respondent	49 years	not known

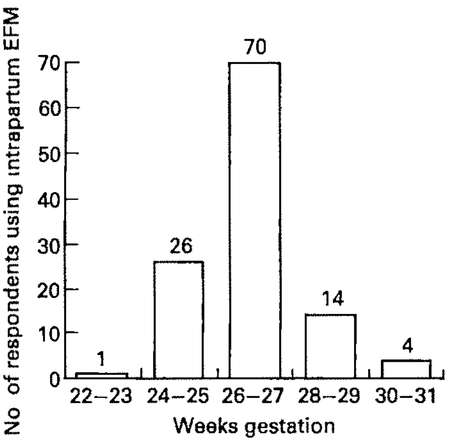

Fig. 1. Question: 'What is the lowest gestational age at which you would normally perform intrapartum electronic fetal heart monitoring?'

When asked to consider the mode of delivery for fetuses in the vertex presentations between 26 and 32 weeks, only 12% ($n=14$) said they practised routine abdominal delivery. This rose to 78% if presentation was by the breech. Despite this, only 35% considered there was satisfactory evidence to support their policy. Dissatisfaction was highest in consultants within 10 years of membership, with only 25% considering the evidence satisfactory, although 69% routinely performed sections. The distribution of the lowest gestations at which a section would be used for the preterm breech was not significantly different from that for the preterm fetus with vertex presentation. Only 9% would use abdominal delivery for the preterm breech at less than 26 weeks (Fig. 3); 18% said they never performed a section for the preterm breech and 3% said that their decision depended on the parity of the woman rather than on the gestational age. Overall, 83% said they might change their practice if a prospective controlled trial showed that this would produce better neonatal results.

Overall, 71% reported that their policy was affected by medicolegal considerations, 17% strongly so. One consultant reported that he was currently involved in litigation in relation to a preterm breech. The proportion affected by medicolegal considerations was 74% (74 of 100) if the membership had been obtained more than 10 years previously, compared with 50% (8 of 16) if $\leq$10 years previously ($\chi^2=3{\cdot}83$, $P<0{\cdot}05$). Consultants who said they were affected by medicolegal considerations were significantly more likely to use abdominal delivery than those not affected (87% *vs* 68%; $\chi^2=5{\cdot}76$, $P<0{\cdot}05$). This effect was not seen in relation to section for other fetal indications nor in relation to the preterm vertex. Despite this, younger consultants (membership for <10 years) were still significantly more likely to use abdominal delivery for the preterm breech at under 26 weeks gestation compared with the older consultants (membership for $\geq$10 years) (82% *vs* 42%; $\chi^2 = 6{\cdot}04$, $P<0{\cdot}01$).

Despite the scanty evidence about the optimum mode of delivery for the woman with a preterm vertex there seems to be general agreement that she should be allowed to deliver vaginally provided the labour is uncomplicated.

The gestation at which clinicians start to use EFM correlates closely with the gestation at

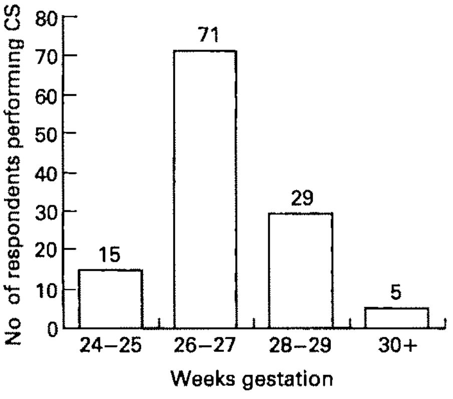

Fig. 2. Question: 'What is the lowest gestational age at which you would usually perform a caesarean section (CS) for fetal indications?'

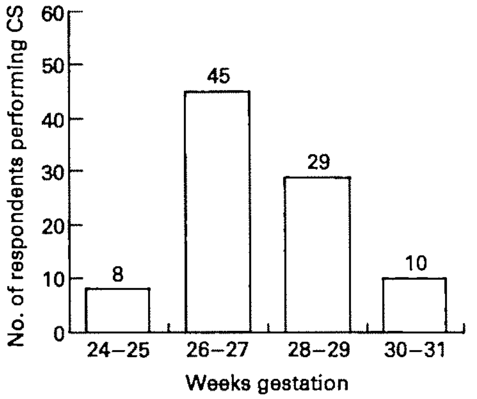

Fig. 3. Question: 'What is the lowest gestation at which you would usually perform a caesarean section (CS) for the otherwise uncomplicated breech presentation in spontaneous labour?'

which they consider caesarean section for fetal indications, although most start to use EFM at a somewhat earlier gestation.

These results demonstrate that a management policy does not have to be scientifically validated before it is taken up into clinical orthodoxy (and later, the obstetric textbook). There may be a belief that in a difficult situation any obstetric intervention is better than none, even when it is of no proven benefit (O'Leary & Paisley 1983). This is likely to be particularly true when there are medicolegal pressures and masterly inactivity may be seen as neglect.

Our findings confirm that the mode of delivery for the woman with a preterm breech is still an area of major clinical controversy, and a randomized prospective trial would not only be welcomed by the profession, but its findings are likely to be implemented.

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Trends in multiple births in Italy: 1955–1983

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Summary. On the basis of the numbers of single and multiple births routinely collected by the Central Institute of Statistics, trends in multiple births in Italy over the period 1955–1983 were analyzed. Between 1955 and 1983 the frequency of multiple births declined by about 25% (from 12·6/1000 deliveries to 9·6/1000 deliveries). The downward trend was constant until the early 1970s when rates tended to level off and increase slightly. This finding was largely attributable to trends in dizygotic rates, monozygotic births being approximately constant over the period considered. Multiple birth rates rose till age 35–39, being more than two times higher in this age group than in teenagers, but flattened off in the subsequent strata of age: this finding was constant over the period considered. Despite the general decreasing trend, the regional differences persisted largely unchanged, multiple birth rates being about 30% higher in Southern (and less developed areas) of the country than in the North of Italy. Geographic differences were limited to dizygotic pregnancies, monozygotic rates being constant (about 4/1000 pregnancies) in various areas.

There have been steady declines in developed countries in the incidence of multiple births in the last three decades. These trends have been restricted to dizygotic twins, while monozygotic rates have been unchanged or have slowly increased (Alberman 1987; James 1972; Elwood 1973; James 1982; Editorial 1976; Bonnelykke *et al.* 1987).

In more recent years, data from the United Kingdom, Denmark, Canada have suggested that the lowering of multiple dizygotic births rates have stopped, and, if any, a slight increase is observed, while triplets have markedly risen from the early 1980s onwards (Botting *et al.* 1987; Elwood 1983; James 1983).

Few data are, however, available on South European Countries. We have therefore considered Italian multiple birth rate trend based on data provided routinely by the Italian Central Institute of Statistics (ISTAT) from 1955 onwards.

Subjects and methods

Numbers of single and multiple pregnancies

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according to maternal age, sex and broad Italian geographic areas (North, Centre, South) for the period 1955–1983 have been obtained by annual publications of the Central Institute of statistics (1955–1979) (ISTAT 1958–1984) or directly by individual records of each Italian birth (for the period 1980–1983) provided on magnetic tape by the same Institute.

On the basis of these data, multiple birth rates were computed according to maternal age and geographic areas for calendar year or quinquennium for the total of multiple births and, in separate strata of unlike sex pregnancies, twin and triplets or more births, maternal age and geographic area. Estimates of dizygotic or monozygotic multiple pregnancies were calculated using the Weinberg's method (Weinberg 1901). At all stages of the analysis the unit of study was the pregnancy (delivery) and not the child(ren). Age-standardized rates were computed using the direct method with the total distribution of births in 1971 as standard. The sex of twin pairs by maternal age was available only for the years 1980–1983.

Results

Between 1955 and 1983, the frequency of multiple births declined from 12·6/1000 deliveries (1 out of 79 deliveries) to 9·6/1000 deliveries (1 out of 104) (Table 1). The downward trend was constant till early 1970s when rates of multiple births tended to level off and to increase slightly in early 1980s. This was largely attributable to trends in dizygotic rates, monozygotic ones being constant over all the period considered (Fig. 1). The proportion of triplets or higher order births on the total of multiple births was constant from 1955 to the early 1970s, but then it rose markedly; for example the ratio between triplets or higher order births and total multiple births was 1:99 in the quinquennium 1955–1959, 1:103 in 1975–1979 and 1:70 in 1980–1983 (Table 1).

Rates of multiple births decreased similarly in the three Italian broad geographic areas (North, Centre, South, Table 1), but the North/South ratio persisted largely unchanged in proportional terms: rates were about 30% higher in the Southern (and less developed) areas of the country. These geographic differences were limited to dizygotic multiple pregnancies, monozygotic rates being approximately constant in various areas and over the study period.

Trends in multiple births in various strata of age are presented in Fig. 2. Multiple birth rates were highest in the age group, being more than twice as high as the under 20 rate, but flattened off in the subsequent strata of age. A decreasing trend over calendar period was consistently observed in all age groups, although slightly more marked in women between 25 and 39 years and less evident in younger and older women (data not shown). An analysis based on age-specific rates for 1980–1983 shows that the differences are more marked for dizygotic multiple pregnancies: the rates in 35–39 years old women were more than threefold higher than in those aged 20 or less. Monozygotic rates were slightly increasing till age 35–39, but the differences were comparatively limited (Table 2).

Discussion

Dizygotic multiple pregnancies rates in Italy declined from early 1950s to early 1970s by about 25%. Then this trend levelled off and a slight increase was observed in the early 1980s. Monozygotic rates were approximately constant over the whole study period. These findings were similar in different strata of maternal age and in the three broad Italian geographic areas (North, Centre, South).

The proportion of triplets or higher order births on the total of multiple pregnancies was about 1 out of 100 from the mid 1950s to the late 1970s, but rose to about 1 out of 70 in the 1980–1983 period.

Similar trends in absolute and relative terms have been reported from North European and American countries (Botting *et al.* 1987; Elwood 1983; James 1983; Métneki & Czeizel 1983). For example in England the frequency of multiple pregnancies was 12·2/1000 pregnancies in 1956–1959, declined to 9·7 in 1976–1980 but increased to 10·2 in 1982–1985, and the estimated monozygotic rate was about 3·5–3·8 over the period 1955–1985 (Botting *et al.* 1987).

Many factors have been claimed to explain the decreasing trends as, for example, changes in the baseline distribution of risk factors such as old maternal age and high parity (Botting *et al.* 1987), nutritional or socioeconomic changes (Alberman 1987), oral contraceptive use (Rice-Wray *et al.* 1971; Rothman 1977; Bracken 1979), secular increases in miscarriage rate or declining in fertility rates/sperm counts (Hemon *et al.* 1979; James 1978; 1980).

Table 1. Trends in multiple births rates according to Italian broad geographic areas, Italy 1955–1983

Geographic area	Calendar period					
	1955–59	1960–64	1965–69	1970–74	1975–79	1980–83
Italy						
No. of multiple pregnancies	56 237	56 517	52 931	43 477	34 774	23 236
Multiple birth rates/1000 pregnancies	12·6	11·8	11·0	9·8	9·3	9·4
Dizygotic rates/1000 pregnancies	8·8	8·1	7·2	6·1	5·4	5·4
Triplets or higher order birth rates/1000 pregnancies	0·13	0·12	0·11	0·09	0.09	0·13
North						
No. multiple pregnancies	18 747	20 127	19 768	16 474	13 028	8 003
Multiple birth rates/1000 pregnancies	12·0	11·0	10·2	9·0	9·1	8·9
Dizygotic rates/1000 pregnancies	8·1	7·2	6·4	5·4	5·0	5·0
Centre						
No multiple pregnancies	8 646	8 854	8 263	7 022	5 780	3 996
Multiple birth rates/1000 pregnancies	12·0	11·1	10·1	9·0	9·0	9·5
Dizygotic rates/1000 pregnancies	8·1	7·3	6·3	5·5	4·9	5·5
South						
No. multiple pregnancies	28 844	27 536	24 900	19 981	15 966	11 237
Multiple birth rates/1000 pregnancies	13·3	12·7	12·1	10·9	9·7	9·7
Dizygotic rates/1000 pregnancies	9·5	9·1	8·3	7·1	5·8	5·8

In relation to these factors, in this study, age-adjusted rates did not markedly differ from crude ones. For example the corresponding crude and standardized multiple births rates were 12·6 and 12·3 in 1955 and 9·6 and 10·1 in 1983. The fertility rate dropped in Italy markedly only from the early 1970s onwards (ISTAT 1974), and the decline of multiple births preceded the use of oral contraception.

Another finding observed in this study, as well in similar analysis from other countries (Botting *et al.* 1987), for which no obvious explanation has been provided, is the U-shaped age distribution of dizygotic births, with a steady rise up to age 35–39 and a subsequent fall. Selection mechanisms, genetic and environmental factors can be suspected, although they are as yet inevitably speculative.

It seems therefore that no single defined factor

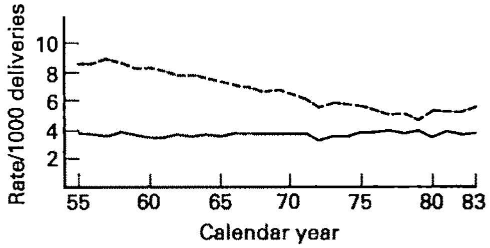

Fig. 1. Trend in dizygotic and monozygotic twin. Italy, 1955–1983. ---- dizygotic pregnancies; —— monozygotic pregnancies.

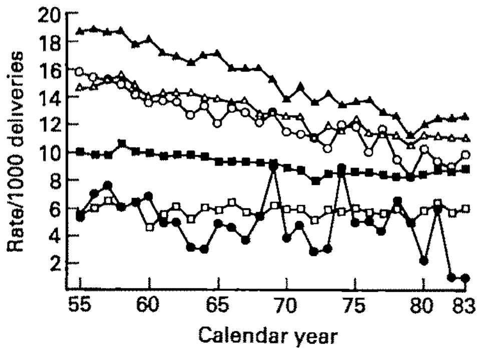

Fig. 2. Trend in multiple birth according to maternal age. Italy, 1955–1983. ●——● ≥45, ○——○ 40–44; ▲——▲ 35–39; △——△ 30–34; ■——■ 20–29; □——□ <20.

Table 2. Multiple birth rates according to maternal age and zygosity, Italy 1980–1983

Maternal age (years)	Total number of deliveries	Multiple births/1000 deliveries	
		Dizygotic	Monozygotic
< 19	159 069	2·5	3·6
20–24	747 066	4·2	3·6
25–29	823 302	5·4	4·2
30–34	505 582	7·3	4·1
35–39	185 916	8·1	4·5
40–44	43 853	6·0	3·8
≥ 45	3 177	n e.*	4·7†

* Not estimated (no unlike sex multiple birth was observed in this strata of age in the considered period).
† Including probably some like sex dizygotic pregnancies.

can explain the trends over time observed, which can only tentatively be related to a complex of more favourable age distribution of births, impaired nutrition and socioeconomic conditions. Such a complex of factors can explain, moreover, the geographic distribution of multiple births within Italy, since rates were persistently higher in Southern areas, where socioeconomic conditions are less favourable, and the number of births in more advanced ages is larger (Parazzini *et al.* 1988a). Further, the absence of a difference in trends according to age groups and geographic trends suggests that the factors affecting dizygotic rates have not been modified in proportional terms, in particular in the three broad Italian geographic areas. Similar findings have also been observed for other perinatal and maternal mortality statistics (Parazzini *et al.* 1988a,b), and in other countries, such as in the United Kingdom, where slopes of trends in multiple births were comparable in different social classes (Murphy & Botting 1989).

An interpretation is, on the other hand, easily available for the increase in triplets and higher order births registered from the early 1980s onward, which should be essentially related to treatments for infertility (Smith 1989). This has probably had some impact, although difficult to quantify, on the changed trends of twin births as well.

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Serum bile acids in normal pregnancy

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Summary. Serum bile acid levels were measured in a longitudinal study of 56 women throughout normal pregnancy. Postprandial levels of serum bile acids were measured at each visit. Mean serum bile acid levels increased significantly from 5·3 (2 SD 3·4) µmol/l at 16 weeks to 6·5 (2 SD 3·7) µmol/l at term ($P<0·005$).

Bile acids are synthesized from cholesterol in the liver. They share the cyclopentano-perhydrophenanthrene nucleus with vitamin D, cholesterol, a variety of steroid hormones and the digitalis glycosides. The primary bile acids, cholic acid (CA) and chenodeoxycholic acid (CDCA) are formed in about equal quantities and conjugated principally with glycine and taurine. The sodium and potassium salts of the acids are secreted in the bile; secondary bile acids are formed by bacterial degradation in the gut. Cholic acid is converted to deoxycholic acid (DCA) and chenodeoxycholic acid to lithocholic acid (LCA). About 90% of the bile acids undergo enterohepatic circulation

Intrahepatic cholestasis of pregnancy (ICP) is a clinical syndrome of generalized pruritus, mild jaundice and intrahepatic cholestasis occurring predominantly in the latter half of pregnancy. There is evidence that the syndrome is associated with increased perinatal mortality and morbidity (Reid *et al.* 1976). An early and accurate identification of these high risk pregnancies is essential.

We have made a longitudinal study of a group of normal pregnant women to determine the normal range for total serum bile acids.

Subjects and methods

Women were recruited from a routine antenatal booking clinic. Women were not included if they had a past history of pruritus of pregnancy, intrahepatic cholestasis of pregnancy, hepatitis, gall bladder disease, jaundice or pruritus on the oral contraceptive pill, heavy alcohol ingestion, had used drugs known to affect hepatobiliary function, or had a family history of cholestatic liver disease. The women were seen in a single antenatal clinic and the standard antenatal examination and investigations were performed at each visit. All had ultrasonography to confirm gestational age. In addition all were tested for hepatitis B surface antigen and had ultrasonography of the liver and gall bladder. The women were seen every 4 weeks from 16 to 28 weeks, then every 2 weeks until 34 weeks and thence weekly until delivery. At each clinic attendance questions were asked regarding symptoms of cholestasis (pruritus, dark urine, pale stools) and drug ingestion and, if answered positively, these women were excluded. Women were asked to attend the morning antenatal clinic after a light breakfast. A sample of postprandial venous blood was collected for total bile acid determination. Total serum bile acids were measured using 3-alpha-hydroxysteroid dehydrogenase (3-alpha-HSD). The only measurable substrates for 3-alpha-HSD in serum are the free bile acids and salts, and their corresponding glycine and taurine conjugates. A control sample assayed on

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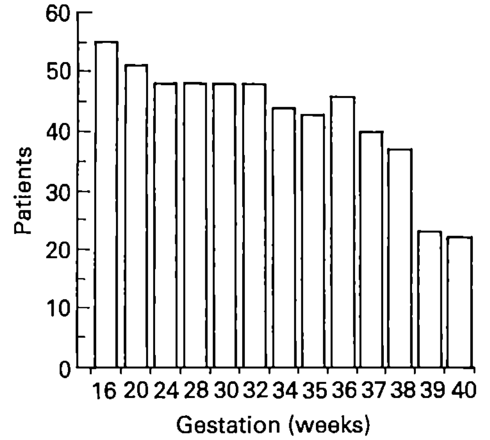

Fig. 1. Number of patients studied at each gestational age.

64 previous occasions yielded a mean value of 23·2 (SD 2·63) μmol/l, giving a coefficient of variation of 11·4.

Statistical calculations were performed using the computer software packages Stat View 512+ (BrainPower, Inc.) and StatWorks (Cricket Software, Inc). For each gestational age, assessment of normality of data was determined by using the Probit plot (Kirkwood 1988) and this was confirmed by using normality testing on the StatWorks program. The method of analysis of data was that of summary measures (Mathews *et al.* 1990). For each patient the slope of the line of regression of serum bile acids against gestational age was determined. The mean slope was then determined and the one sample *t*-test performed to determine if the change throughout pregnancy was significant. The reference range was determined by calculating the mean ±2 SD.

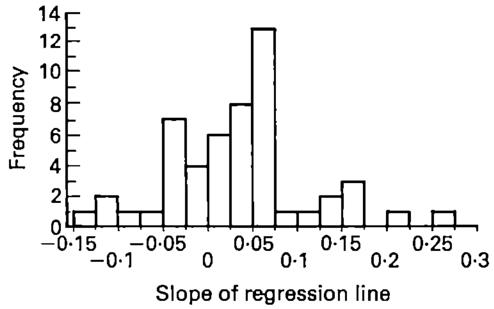

Fig. 2. Frequency histogram of gradient of regression line of serum bile acids.

Results

Fifty-six women were followed throughout pregnancy. Their average age was 26 years (range 17–42). Twenty-six were primigravidas and 30 were multigravidas. The mean gestation at delivery was 39·4 weeks (range 37–41). Forty-six had vaginal deliveries, six had forceps deliveries and four had caesarean sections. Mean blood loss at delivery was 265 ml (range 100–1500). The mean birthweight was 3435 g (range 2600–4915) with mean 1 and 5 min Apgar scores of 7 and 9 respectively. The number of women studied at each gestational age is shown in Fig. 1. Statistical analysis confirmed normality of data, using both normality testing on the StatWorks program and Probit method. The slope of the regression line of serum bile acids on time was calculated for each patient. A frequency histogram describing the slope of these regression lines for each patient is shown in Fig. 2. Forty patients had a positive slope and 16 patients had a negative slope. The mean slope of the regression lines for all patients is 0·035 (SE 0·011) and increased significantly throughout pregnancy ($P<0·005$). Mean serum bile acid levels increased from 5·3 (2 SD 3·4) μmol/l at 16 weeks to 6·5 (2SD 3·8) μmol/l at term (Table 1).

Discussion

Intrahepatic cholestasis of pregnancy is a clinical syndrome of pruritus and jaundice occurring in the latter half of pregnancy with clearing of symptoms in the early postpartum period. The symptoms usually return in subsequent pregnancies. Biochemical investigation of these

Table 1. Mean serum bile acid levels ±2 SD throughout pregnancy

Gestational age (weeks)	Serum bile acid levels (μmol/l)		
	Mean	Mean −2 SD	Mean +2 SD
16	5·3	1·9	8·7
20	5·1	2·3	7·9
24	5·1	1·9	8·3
28	5·7	2·3	9·1
32	5·6	2·4	8·8
34	5·4	2·8	8·0
35	5·6	2·2	9·0
36	5·7	2·7	8·7
37	5·9	2·7	9·1
38	6·0	2·2	9·8
39	6·5	1·7	11·3
40	6·5	2·7	10·3

patients shows a mild elevation of serum transaminases, elevated serum bilirubin, alkaline phosphatase, serum cholesterol and a 10 to 100 fold increase in serum bile acids.

It is now apparent that 'pruritus gravidarum' is a milder form of the disease. Jaundice and standard biochemical evidence of cholestatic liver function are usually not present. Serum bile acid levels are increased in pruritus gravidarum, and are a more sensitive method of detecting intrahepatic cholestasis. The increase in serum bile acids may occur 2 or more weeks before the onset of symptoms and abnormalities in standard liver function tests (Tikkanen & Adlercreutz 1973).

Confusing data exist regarding the effect of pregnancy on liver function. Reduced biliary exretion of bromsulphalein has been reported in the last trimester. This has led to the suggestion that normal pregnancy is associated with mild subclinical cholestasis possibly due to high concentrations of circulating steroid hormones (Simcock & Forster 1967). Samuelson & Thomassen (1980) found a poor correlation between levels of serum aminotransferases, alkaline phosphatase and bilirubin and levels of serum cholic and chenodeoxycholic acid. Laatikainen & Hesso (1975) similarly found no statistical significant correlation between total bile acid levels and levels of serum aminotransferase, alkaline phosphatase and total bilirubin indicating that total bile acid levels give additional information on the disturbance of liver function in intrahepatic cholestasis of pregnancy. Conversely Lunzer *et al.* (1986) assessed changes in 'conventional' biochemical liver function tests and found elevated cholylglycine levels correlated with serum transaminase and serum cholesterol concentrations, while other liver functions correlated poorly with serum cholyglycine levels.

Individual bile acid levels have been measured by gas liquid chromatography, RIA and more recently by the 3-alpha hydroxysteroid dehydrogenase methods in normal and cholestatic pregnancies (Heikkinen 1983; Samuelson & Thomassen 1980; Laatikainen & Hesso 1975).

Using gas liquid chromography Laatikainen & Hesso (1975) found the mean total amount of cholic, chenodeoxycholic and deoxycholic acids in a group of healthy fasting women was 2·14 µmol/l, in a group of fasting pregnant women in early pregnancy 1·13 µmol/l and in late pregnancy 2·10 µmol/l.

Samuelson & Thomassen (1980) used RIA to quantitate the conjugates of cholic and chenodeoxycholic acid in normal pregnancy and also found levels to be within the normal range throughout uncomplicated pregnancy. This method measures the total amounts of glycine and taurine conjugates and about 50% of the unconjugated bile acids, but not the sulfated bile acids Heikkinen (1983) using RIA measured blood levels of cholic acid, chenodeoxycholic acid and deoxycholic acid. In healthy pregnant patients, only chenodeoxycholic acid significantly increased ($P<0{\cdot}05$) throughout pregnancy. Fulton *et al.* (1983) using RIA found fasting cholate concentrations significantly increased by 34 weeks and remaining so up to 6 weeks postpartum. The concentrations of chenodeoxycholate remained unchanged. The ratio of fasting cholate: chenodeoxycholate rose from 1·1:1·0 at 29 weeks to 1·9:1·0 at 38 weeks.

This is in agreement with Sjovell & Sjovell (1986) who found as pregnancy progressed, increasing concentrations of plasma bile acids were associated with an increase in the relative amount of cholate to chenodeoxycholate. It is difficult to explain the discrepancies between these results and those of Heikkinen (1983) who reported only a rise in chenodeoxycholic acid. More recently Lunzer *et al.* (1986), using a commercially available RIA for estimating the glycine conjugate of cholic acid, found a normal nonpregnant range for 2-h postprandial serum cholyglycine of 0–1·5 µmol/l. In normal pregnancy serum cholyglycine rose progressively from a median concentration of 0·3 µmol/l in early pregnancy to 0·7 µmol/l in late pregnancy. Although this rise remained well within the normal range, the increase was statistically significant ($P<0{\cdot}05$).

Application of the enzymatic method using 3-alpha-hydroxysteroid dehydrogenase (3-alpha-HSD) and fluorometric measurement of the generated NADH for estimation of serum bile acids was introduced in 1970 by Murphy *et al.* (1970). Briisgaard *et al.* (1979) measured total 3-alpha-hydroxy bile acids by this method in normal nonpregnant subjects and found mean levels of 3·0 (SD 1·1) µmol/l. Laatikainen & Tulenheimo (1984) measured total 3 alpha-hydroxy bile acids in 60 uncomplicated pregnancies and found a mean value of 1·96 (SE 1·56) µmol/l (range 0–5 µmol/l). The method was controlled by analysing samples using a gas chromatographic method. The total 3 alpha-hydroxy bile acid value was 32% higher than the total amount of cholic, chenodeoxycholic and deoxycholic acids obtained by the gas chromatographic method. Schwarz *et al.* (1974) measured total 3-alpha-hydroxy bile acids in the serum in normal pregnancy and found a mean value of 5·5 µmol/l (range 3·6–9·3 µmol/l), which is similar to the results in this study but significantly higher than those reported by Laatikainen & Tulenheimo (1984) (11). They also found that deoxycholic acid predominated in early pregnancy and cholic acid was the predominating bile acid in late pregnancy.

In our study postprandial venous samples were used for measuring total bile acid levels. It has been shown the metabolic clearance varies for the individual bile acids (Samuelson & Thomassen 1980). Cholic acid peaks after a fatty meal at 60–90 min and rapidly declines, while chenodeoxycholic acid levels increase more rapidly with a high peak after 30–60 min and decline slowly to fasting levels. The possible postprandial increase in plasma bile acids in the normal nonpregnant state is very low (in the order of 20%).

Obstetricians need to be aware that healthy pregnant women have increased levels of bile acids when assessing women who may have a cholestatic pregnancy. They need to know that the method used for the determination of serum bile acids is affected not only by whether she is fasting or nonfasting state but also by whether individual or total bile acids are measured and also by the technique used. I measured postprandial total serum bile acids by the 3-alpha-HSD method, and found mean serum bile acid levels of 5·3 (2 SD 3·4) µmol/l at 16 weeks increasing to 6·5 (2SD 3·7) µmol/l at term.

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The use of the GnRH analogue buserelin for IVF—does it improve fertility?

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Abstract

Objective—To determine the effect of a short course of the GnRH analogue buserelin and human menopausal gonadotrophin (hMG), for ovarian stimulation in our IVF programme, on reproductive endocrinology and pregnancy rates compared with conventional clomiphene citrate and hMG treatment.
Design—Prospective randomized allocation to one of two ovulation stimulation regimens.
Setting—Fertility clinic.
Subjects—373 infertile couples with various factors associated with their subfertility. All the women were <46 years of age and had normal menstrual cycles.
Intervention—The first group ($n = 151$) was given clomiphene citrate (CC) from days 2–6 of the menstrual cycle and hMG from day 5 onwards (CC/hMG). The second group ($n = 222$) was given buserelin from days 1–3 and hMG from day 2 (buserelin/hMG).
Main outcome measures—Concentration of plasma luteinizing hormone (LH), oestradiol (E_2) and progesterone, number of ovulatory follicles induced and the occurrence of pregnancy.
Results—Plasma LH, E_2 and progesterone concentrations were reduced in the late follicular phase after buserelin/hMG compared with CC/hMG. Buserelin/hMG promoted the development of more follicles than CC/hMG. The overall pregnancy rate after buserelin/hMG was not significantly different from that following CC/hMG treatment.
Conclusion—The chance of pregnancy is not improved by the short-term use of buserelin with hMG, provided adequate follicular phase management is maintained.

The use of the gonadotrophin releasing hormone (GnRH) analogue (buserelin) combined with human menopausal gonadotrophin (hMG) has become increasingly popular in the management of the menstrual cycle for in vitro fertilization (IVF) programmes. One of the reasons for this lies in the capacity of the agonist to recruit relatively large numbers of follicles, consequently increasing the availability of embryos for replacement and freezing, while eliminating detrimental high tonic luteinizing hormone (LH) levels and the spontaneous LH surge. Complete suppression of endogenous gonadotrophin secretion during long-term administration of buserelin necessitates the use of significantly higher doses of hMG to achieve adequate follicular growth, and continued pitui-

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tary desensitization after the cessation of treatment may lead to inadequate luteal function (Smitz *et al.* 1987). The short-term use of the analogue, however, could overcome the problems associated with prolonged desensitization of the pituitary by only partially suppressing endogenous LH secretion. The policy of this clinic has been to maintain an individual approach to follicular stimulation; women with regular menstrual cycles being administered clomiphene citrate and hMG (CC/hMG) only. However, the putative advantages of using a short course of buserelin with hMG led us to investigate the benefits of using this regimen compared with that of CC/hMG.

Subjects and methods

Women up to 46 years of age were admitted to the clinic with various causes of infertility; many couples had two or more factors associated with their subfertility (Table 1). The mean age and distribution of attributed cause of infertility was similar in both treatment groups.

Women with ovulatory cycles of normal length who were either undergoing IVF treatment for the first time, or who had had previous satisfactory follicular response to clomiphene citrate and hMG, were assigned to one of two treatment groups. Allocation was by chance by two clinicians acting independently, the women were not selected for a particular treatment because of any particular clinical characteristic.

One group underwent follicular stimulation induced with 100 mg clomiphene citrate (Clomid; Merill National Laboratories), commencing on day 2 of the cycle for 5 days and hMG (Pergonal, Serono), two ampoules (75 IU LH + 75 IU FSH/ampoule) daily intramuscularly from day 5 of the cycle. The second group received the alternative treatment of 500 µg buserelin (Suprefact, Hoechst) subcutaneously from days 1–3 and hMG, three ampoules from day 2 onwards. These doses of hMG generally induced a suitable follicular response; however, for both regimens, the daily quantity of hMG administered was tailored to individual needs, therefore the amount of hMG given ranged from 1–3 ampoules per day for those treated with clomiphene and 2–6 per day for those given buserelin

Ovulation was induced with 10 000 IU of human chorionic gonadotrophin (hCG: Pregnyl, Organon Laboratories). If there was an endogenous LH surge, the hCG was given as soon as the surge was detected. To detect the LH surge, excreted LH levels were measured in each of eight urine samples produced at regular intervals during a given 24-h period (LH Maiaclone, Serono). The follicular phase was monitored

Table 1. Age and cause of infertility of women treated with either CC/hMG or buserelin/hMG

	CC/hMG	Buserelin/hMG
No. of women	151	222
Age (years) mean (SEM)	33·2 (0·4)	34·2 (0·3)
Cause of infertility *n* (%)		
Female		
Oviduct	78	93
Endometriosis	6	6
Cycle disorder	2	9
Sperm antibodies/cervical hostility	5	8
Total	91 (60)	116 (52)
Male		
Oligozoospermia	9	7
Asthenozoospermia	5	13
Oligoasthenozoospermia	2	9
Azoospermia	4	8
Immunological/other	6	5
Total	26 (17)	42 (19)
Male and female	29 (19)	49 (22)
Idiopathic	5 (3)	15 (7)

CC = clomiphene citrate; hMG = human menopausal gonadotrophin.

Table 2. Outcome of treatment cycles of women treated with CC/hMG or buserelin/hMG

	CC/hMG	Buserelin/hMG
No. of treatment cycles started	151	222
No. discharged prior to oocyte recovery	31 (21)	62 (28)
No starting an LH surge	47 (31)	7 (3)
No. of oocyte recoveries	115 (76)	160 (72)
No. of embryo replacements	110 (73)	151 (68)
No. (%) of replacements with		
one embryo transferred	8 (7)	7 (5)
two embryos transferred	17 (16)	18 (12)
three embryos transferred	68 (62)	109 (72)
four embryos transferred	17 (15)	17 (11)

CC = clomiphene citrate, hMG = human menopausal gonadotrophin. Results are *n* (%) values.

daily by assessing conjugated oestrogens fluorometrically in 24-h collections of urine and a single daily plasma sample was used to measure oestradiol -17β (E_2, Maiaclone, Serono, LH (LH Maiaclone, Serono) and progesterone (IDS, Washington). Daily ultrasonographic measurements were made to assess follicular growth.

Oocytes were recovered 34–35 h after the administration of hCG or 26–23 h after the detection of the LH surge in urine. Follicular aspiration, IVF techniques and the method of embryo transfer have been reported previously (Fishel & Jackson 1986; Webster 1986). In line with the British Interim Licensing Authority's recommendations, a maximum number of three embryos was transferred, except in exceptional cases. Pregnancy was confirmed by consecutive rises in β-hCG (concept β, enzyme-linked immunosobent assay (ELISA) monoclonal assay RIA) and the presence of a gestational sac on ultrasound 5 weeks after embryo replacement.

Statistical analysis of data used the unpaired Student's *t*-test and χ^2 analysis where appropriate.

Results

The outcome of treatment cycles is shown in Table 2. A similar overall percentage of women were discharged before oocyte recovery in both treatment groups [31/151 (21%) *vs* 62/222 (28%)] for CC/hMG and buserelin/hMG respectively ($\chi^2 = 2{\cdot}25$, $P = 0{\cdot}13$). The majority of women having the CC/hMG treatment were discharged because they had a poor or inappropriate response [25/31 (81%)] (of these, 13/25 (52%) had started an endogenous LH surge) and few because they did not respond at all [6/31 (19%)]. By contrast, significantly ($\chi^2 = 4{\cdot}28$, $P = 0{\cdot}039$) more women having the buserelin/hMG treatment were discharged because they did not respond [27/62 (44%)] and fewer women ($\chi^2 = 4{\cdot}28$, $P = 0{\cdot}039$) because they had a poor or inappropriate response [35/62 (57%)] (only 4/35 (11%) had started an LH surge). Signifi-

Table 3. A comparison of plasma hormone concentrations in women treated with CC/hMG or buserelin/hMG

	n	CC/hMG	*n*	Buserelin/ hMG	Significance	
					P	*t*
Oestradiol (pmol/l)	115	4746 (186)	154*	3920 (125)	0·001	3·816
Progesterone (pmol/l)	115	4463 (255)	154	3382 (162)	0·001	3·727
LH (iu/l)	30	6·2 (0·5)	43	1·3 (0·1)	0·001	10·536

Results are mean (SEM) values measured on the day of hCG The LH value represents the overall mean measured on the day of hCG and the three preceding days for those women with all four LH values.

*Of the women who had oocyte recovery, data on both plasma oestradiol and progesterone concentrations were unavailable for 6 women

Table 4. No of ovulatory follicles present at oocyte recovery and steroid concentration per follicle in women treated with CC/hMG or buserelin/hMG

	CC/hMG ($n = 108$)	Buserelin/hMG ($n = 152$)	Significance P	 t
Steroid concentration/ovulatory follicle				
Oestradiol (pmol/l)	694·3 (27·0)	476·8 (17·5)	0·001	7·064
Progesterone (pmol/l)	647·2 (39·1)	459·9 (32·3)	0·001	3·705
No of ovulatory follicles	7·5 (0·3)	9·3 (0·3)	0 001	3·775

Results are mean (SEM) values.
CC = clomiphene citrate, hMG = human menopausal gonadotrophin.

cantly fewer women started an endogenous LH surge on the buserelin/hMG treatment (47/151 *vs* 7/222, $\chi^2 = 54{\cdot}54$, $P<0{\cdot}001$). The number of women reaching oocyte recovery and embryo transfer was similar for both regimens, as was the percentage of women having one, two, three or four embryos replaced.

A comparison of endocrine data between the two treatment groups is shown in Table 3. Women in the CC/hMG group had significantly ($P = 0{\cdot}001$) higher plasma oestradiol-17β and progesterone concentrations on the day of hCG than those in the buserelin/hMG group. Treatment with buserelin/hMG stimulated the development of more ovulatory follicles than treatment with CC/hMG so that steroid concentrations per ovulatory follicle were considerably less in the buserelin/hMG group than in the CC/hMG group (Table 4).

Overall mean plasma LH levels (Table 3) were significantly ($P = 0{\cdot}001$) higher in those treated with CC/hMG than in those treated with buserelin/hMG. Data from women in whom a spontaneous LH surge had begun were excluded from this analysis as were those who did not have LH values measured on the day of hCG and *all* 3 preceding days.

The pregnancy rates following embryo replacement are shown in Table 5. The overall percentage of women achieving a pregnancy after short-term treatment with buserelin/hMG [57/151 (38%)] was not significantly different from those treated with CC/hMG [38/110 (35%)].

The outcome of the pregnancies is shown in Table 6. The proportions of miscarriages, multiple pregnancies and live deliveries did not differ between the two treatment groups.

Discussion

Our results confirm that plasma LH levels are markedly reduced in women treated with buserelin/hMG and this is reflected in the relative suppression of follicular steroid secretion The administration of buserelin enhances gonadotrophin secretion in the first instance, depleting pituitary gonadotrophin stores and causing pituitary desensitization and receptor loss (Sandow *et al.* 1987). The continued suppression of endogenous LH may, in itself, account for the relatively low output of oestradiol and progesterone by the follicle; however, the initial exposure of the ovarian cells to increased gonadotrophin secretion during the early follicular phase could also lead to the saturation and sub-

Table 5. Pregnancy rate in women treated with CC/hMG or buserelin/hMG [no. pregnant/total (%)]

	CC/hMG	Buserelin/hMG	Combined
No. of embryos replaced			
1	2/8 (25)	2/7 (29)	4/15 (27)
2	3/17 (18)	4/18 (22)	7/35 (20)
3	29/68 (43)	41/109 (38)	70/177 (40)
4	4/17 (24)	10/17 (59)	14/34 (41)
Total	38/110 (35)*	57/151 (38)*	95/261 (36)

*$P = 0{\cdot}688$, $\chi^2 = 0{\cdot}16$.

Table 6. Outcome of pregnancies achieved with CC/hMG or buserelin/hMG treatment [*n*(%)]

	CC/hMG	Buserelin/hMG
Pregnancies	38	57
Miscarriages	5 (13)	16 (28)
Ectopics	3 (8)	3 (5)
Twin pregnancies	6 (16)	13 (23)
Triplet pregnancies	2 (5)	3 (5)
Deliveries	30 (79)	38 (67)
Deliveries with still birth/ neonatal death	0	4
Healthy babies born	40	47

sequent down-regulation of follicular gonadotrophin receptors. Since gonadotrophins and oestradiol itself are needed to induce and maintain follicular LH receptors (Richards *et al.* 1976), a reduction in basal levels of LH could mean that the follicle never fully recovers its full complement of receptors. By contrast, pituitary gonadotrophes are able to regenerate their receptor content as evidenced by the increased proportion of women having an endogenous LH surge when the follicular phase is prolonged.

The present data demonstrate little difference in the occurrence of pregnancy in women treated with buserelin/hMG compared with those stimulated with CC/hMG. However, there may be particular advantages in using one treatment over the other. One obvious benefit of using buserelin is that it is convenient since it inhibits the LH surge and follicular phase monitoring can be reduced. By recruiting larger numbers of follicles, the buserelin/hMG regimen also increases the availability of embryos for replacement and freezing. Buserelin treatment would be of particular advantage to older women who are more difficult to stimulate and tend to have elevated tonic LH levels with conventional CC/hMG treatment.

Even in the short-term, the use of GnRH analogues requires high doses of gonadotrophins to achieve an adequate follicular response. This could be costly, not only in financial terms, but in terms of risk to patient health as the use of high doses of potent follicular stimulants increases the chance of ovarian hyperstimulation (Forman *et al.* 1990; Bellaish-Allart *et al.* 1988). Over many years of using clomiphene citrate and hMG, we have not experienced a single serious case of clinical ovarian hyperstimulation syndrome; but since the beginning of this study we can report five women with severe ovarian hyperstimulation resulting from the short-term use of GnRH analogue with hMG, together with several women with mild to moderate hyperstimulation. Since we and others (Forman *et al.* 1990) have found that the more serious cases of ovarian hyperstimulation are generally precipitated by hCG used for ovulation induction or of embryonic origin, the situation may be avoided by not proceeding to oocyte recovery or not replacing embryos but freezing them for replacement in a subsequent cycle. Severe hyperstimulation in women on the long course of GnRH analogue can also be alleviated by maintaining pituitary desensitization, this option is not available to women treated on a short-term basis. Furthermore, increased gonadotrophin administration, raised oestrogen concentrations and multiple ovulations could make normally menstruating women more prone to abnormal changes in ovarian tissue (Fishel & Jackson 1989), i.e., ovarian hyperactivity may initiate or accelerate previously established neoplastic changes in the ovary.

Contrary to recent claims (Macnamee *et al.* 1989) our data indicate that, when compared with the standard CC/hMG regimen, the short-term use of buserelin combined with hMG does not improve the chances of pregnancy provided adequate follicular phase management is maintained. Macnamee *et al.* (1989) report a pregnancy rate following embryo replacement of only 21% for those treated with CC/hMG. They also state that only 8% of women in this group are discharged due to a poor response before oocyte recovery. Early data from Bourn Hall showed that a high pregnancy rate (34% for 3 embryos replaced, 26% overall) for CC/hMG was associated with more than 25% of cycles abandoned in the follicular phase (Fishel *et al.* 1985) which confirms our current experience, using CC/hMG, 43% for 3 embryos replaced, 35% overall, with 21% of cycles abandoned. This shows that the ostensibly higher pregnancy rate using buserelin is not a function of inherent physiological factors per se, but one of efficient follicular phase management. In view of these data, and the possible risks attached to using GnRH analogues, our clinic has returned to the policy of using the milder follicular stimulation with CC/hMG for women with normal menstrual cycles but at the same time maintaining our individualized approach to treatment.

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Results with the EMA/CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine) regimen in high risk gestational trophoblastic tumours, 1979 to 1989

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Abstract

Objective—To assess the efficacy, toxicity and survival in patients with high risk GTT treated with the EMA/CO regimen (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine/oncovine).
Design—Open non-randomized study of 148 consecutive patients referred to the Charing Cross Hospital between 1979 and 1989.
Setting—Trophoblastic disease centre in a London teaching hospital.
Subjects—148 consecutive patients with high risk GTT were treated with the EMA/CO regimen. 76 patients had received no prior chemotherapy and 72 had received prior chemotherapy.
Main outcome measures—Survival, causes of treatment failure and toxicity were analysed.
Results—Of 76 patients who had received no prior chemotherapy, 62 (82%) are in remission, 72 patients had received prior chemotherapy and 64 (89%) are in remission; an overall survival of 85% for the 148 patients. Ten of the 76 patients without prior chemotherapy died from extensive disease within 3 weeks of starting chemotherapy. The complete and partial response rates to EMA/CO chemotherapy were 80% and 18% respectively. The addition of cisplatin salvaged 9 of 11 (82%) who developed drug resistance and did not require surgery. Salvage surgery alone resulted in 7 of 8 (87%) having complete remissions. Relapse after EMA/CO chemotherapy is uncommon (5·4%) but survival is still relatively good with further chemotherapy and/or surgery with 6 (75%) of 8 patients obtaining a further sustained remission. Complications from EMA/CO chemotherapy are acceptable with myelosuppression being dose-limiting. Late sequelae are uncommon: menstruation usually returns with a few months, and no fetal abnormalities have been recorded in subsequent pregnancies. One patient developed what we presume to be a therapy-induced acute myeloid leukaemia.
Conclusion—At present EMA/CO chemotherapy is our treatment of choice for patients with high risk GTT. Its toxicity is predictable and reversible. In patients developing drug resistance, salvage surgery is important. Future developments may include further dose intensification with the addition of haemopoietic growth factors, earlier diagnosis and the separation of gestational from non-gestational trophoblastic tumours.

The survival of patients with gestational trophoblastic tumours (GTT) is now excellent provided clinicians are constantly aware of this potential diagnosis and refer patients to centres specializing in their treatment. The commonest prodrome to a GTT is a pregnancy with a hydatidiform mole. A registration scheme for all those patients who are at risk of requiring treatment has been established in the UK since 1973 (Bagshawe *et al.* 1986). All patients should be monitored closely with serial human chorionic gonadotrophin (hCG) concentrations. This approach ensures that very few patients who

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Table 1. Scoring system for gestational trophoblastic tumours* (1.8.83)

	0	1	2	6
Age (years)	<39	>39		
Antecedent pregnancy (AP)	Mole	Miscarriage or unknown	Term	
Interval (end of AP to chemotherapy at CXH) (months)	<4	4–7	7–12	>12
hCG (IU/l)	10^3–10^4	<10^3	10^4–10^5	>10^5
ABO blood group (woman×partner)		A×O O×A O or A× unknown	B×A or O AB×A or O	
No of metastases	Nil	1–4	4–8	>8
Site of metastases	Not detected lungs vagina	Spleen kidney	GI tract liver	Brain
Largest tumour mass (cm)	<3	3–5	>5	
Previous chemotherapy	Nil		Single drug	Two or more drugs

* Low risk = 0–5; medium risk = 6–9; high risk = >9.
CXH, Charing Cross Hospital, GI, gastrointestinal.

have had molar pregnancies and who have been registered should fall into the high risk group (Bagshawe 1976). In patients falling into the low risk group, no patient should die of drug-resistant tumour as is shown in our results between 1974 and 1986 in 361 patients (Bagshawe *et al.* 1989). Since the routine use of etoposide in 1979 in the initial treatment of patients in the medium risk category of this disease, there have been no deaths in 90 patients; the first part of this series was reported up to 1984 by Newlands *et al.* (1986). By definition the main therapeutic problems remain in the high risk group of patients. We reported the initial experience between 1979 and 1984 with the EMA/CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine/oncovine) regimen when we had treated 67 patients and at that analysis 84% of the patients were alive and in remission (Newlands *et al.* 1986). We subsequently analysed 25 patients with CNS metastases and 72% are in remission (Rustin *et al.* 1989). The successful use of EMA/CO has also been reported by Bolis *et al.* (1989) with an 81% survival in 36 patients.

Table 2. Early deaths[1]

Patient	Antecedent pregnancy (AP)	Interval from AP (months)	Days from admission to death	Cause of death
1	Miscarriage	6	7	Respiratory failure
2	Miscarriage	6	14	Respiratory failure
3	Livebirth	7	6	Respiratory failure
4	Livebirth	180[2]	4	Respiratory failure
5	Miscarriage	48	15	Respiratory failure
6	Livebirth	4	2	Cerebral metastases
7	Livebirth	7	8	Cerebral metastases
8	Stillbirth	12	7	Cerebral infarct
9	Livebirth	24	4	Hepatic failure
10	Livebirth[3]	24	2	Pulmonary embolus

[1] = Deaths occurring within 3 weeks of starting chemotherapy
[2] = Hysterectomy 15 years prior to admission.
[3] = Hydatidiform mole 72 months prior to chemotherapy, then 2 normal pregnancies following the mole.

Table 3. Treatment schedules for gestational trophoblastic tumours

Course A EMA		
Day 1.	Etoposide	100 mg/m^2 i.v infusion over 30 min
	Methotrexate	300 mg/m^2 i.v as a 12-h infusion
	Actinomycin D	0·5 mg i.v statim
Day 2.	Etoposide	100 mg/m^2 i.v. infusion over 30 min
	Actinomycin D	0·5 mg i.v. statim
	Folinic acid	15 mg by month/i.m. twice daily for 4 doses starting 24 h after the start of methotrexate
Course B CO		
Day 1	Vincristine	1·0 mg/m^2 i v statim
	Cyclophosphamide	600 mg/m^2 i v infusion over 30 min
Course C EP		
Day 1.	Etoposide	150 mg/m^2 i.v. over 1 h
	Cis-platinum	75 mg/m^2 i v over 12 h with 2 g of $MgSO_4$

Patients and methods

Patient eligibility

All patients falling into the high risk category (Table 1) of GTT presenting to the Charing Cross Centre between 1979 and 1989 are included in this series. Of these 148 patients, 27 (18%) presented following a non-molar miscarriage, 53 (36%) following a term delivery and 68 (46%) following a hydatidiform mole. Only 12 of the 68 patients who presented following a molar abortion and were registered on the UK hydatidiform mole follow-up scheme, had high risk disease. The other 56 patients were either referred from abroad after previous treatment or had relapsed after previous treatment at the Charing Cross. Table 1 is a modification of that proposed by Bagshawe (1976), which puts greater emphasis on the interval from the antecedent pregnancy as an adverse prognostic factor. Ten patients are included in the survival analysis who died early, primarily from initial tumour extent (Table 2) and could not be assessed for response to EMA/CO chemotherapy.

Treatment protocol

The EMA/CO schedule of chemotherapy is shown in Table 3.

EMA is alternated with CO, courses being repeated at 6-day intervals from day 1 (i.e., weekly). Intervals between courses of chemotherapy were not increased unless the leucocyte count fell to less than $1{\cdot}5\times10^9$/l and platelets less than $75\,000\times10^9$/l or mucositis developed. Patients receiving cranial prophylaxis received methotrexate 12·5 mg intrathecally on the day they received CO chemotherapy (i.e., each alternate course). Patients with CNS metastases received an increased dose of systemic methotrexate at 1 g/m^2 as an i.v. infusion over 24 h, followed by folinic acid 15 mg by mouth/i.m. eight-hourly for nine doses starting 32 h after the start of methotrexate therapy (Newlands *et al* 1986).

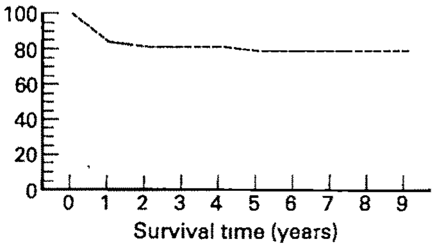

Fig. 1. Survival of 76 patients with gestational trophoblastic tumours treated with the EMA/CO regimen and no prior chemotherapy Cumulative percentage surviving = 78·82%.

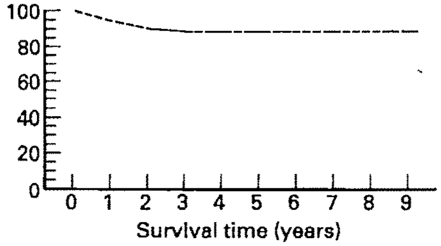

Fig. 2. Survival of 72 patients with gestational trophoblastic tumours treated with the EMA/CO regimen after prior chemotherapy. Cumulative percentage surviving = 88·56%.

Table 4. Overall survival of high risk patients entering EMA/CO series (Nov. 1989)

	No. prior chemotherapy (%)	Prior chemotherapy (%)	Total series (%)
Total	76	72	148
Alive	62 (82)	64 (89)	126 (85)
Dead	14 (18)	8 (11)	22 (15)
Relapsed	2 (2·6)*	6 (8·3)†	8 (5·4)

* Both alive and well after further treatment.

† Four patients are alive and well.

In patients becoming resistant to EMA/CO, the EP schedule (shown in Table 3 as course C) replaced CO chemotherapy: EP alternates at weekly intervals with EMA.

Patient monitoring

Serum hCG was measured twice weekly with an automated radioimmunoassay using an antiserum specific for the beta subunit of hCG which is able to measure 2 IU of hCG/l (approximately equal to 0·5 ng/ml). CSF hCG was measured initially in all patients to exclude brain metastases (Bagshawe & Harland1976).

Definition of response

Responses in GTT are primarily determined by the fall in the serial serum hCG concentrations following therapy Partial responses are defined as hCG fell by more than 1 log following therapy and complete responses are defined as persistently normal hCG concentrations following therapy.

Results

Between 1979 and 1989, 148 consecutive patients were treated with EMA/CO chemotherapy; 76 of them had received no prior chemotherapy and 72 had received prior chemotherapy. Life table analysis of survival in these two groups is shown in Figs. 1 and 2. With a maximum follow-up of 9 years there have been no deaths from disease occurring beyond 25 months from starting chemotherapy (the death in Fig. 1 at 3+ years was from a traffic accident). The current status of these two groups is also shown in Table 4. The responses to EMA/CO chemotherapy have been analysed, excluding the 10 patients who died before a response to the chemotherapy could be assessed. In Table 5 the complete remission to EMA/CO alone was 80% overall with very similar complete and partial response rates in both the prior therapy and no prior therapy groups.

Some patients became resistant to EMA/CO chemotherapy as indicated by a plateau or rise in hCG concentrations. Most of these patients were treated with a modification of the EMA/CO regimen by adding cis-platinum (EP/

Table 5. Response rate of high risk GTT to EMA/CO chemotherapy

	No prior chemotherapy (%)	Prior chemotherapy (%)	Both groups (%)
Complete response	53 (80)	57 (79)	110 (80)
Partial response	13 (20)	12 (17)	25 (18)
No change	—	3 (4)	3 (2·2)
Dead	4 (6)	8 (11)	12 (8·6)
Alive	62 (94)	64 (89)	126 (91·3)
Total	66	72	138
Follow-up (months)			
Range	2–112	4–99	2–112
Mean	50·2	50·6	50·4

The 10 patients who died from initial disease extent (Table 2) before response to EMA/CO could be assessed are excluded from this table.

Table 6. Additional treatment in patients not achieving complete remission to EMA/CO chemotherapy

	Cis-platinum in addition to other chemotherapy (%)		Surgery alone (%)	All patients (%)
	Alone	+ Surgery		
No prior chemotherapy				
Complete remission	5 (83)	5 (83)	2 (67)	12 (80)
Died	1	1	1	3 (20)
Total	6	6	3	15
Prior chemotherapy				
Complete remission	4 (80)	9 (64)	5 (100)	18 (75)
Died	1	5 (36)	0	6 (25)
Total	5	14	5	24

EMA, see Patients and methods). The results of this cis-platinum-containing chemotherapy are shown in Table 6. Analysis of this subgroup in retrospect is difficult. Rising hCG concentrations after an initial fall on chemotherapy in this disease is unequivocal evidence of tumour growth. However, in many of these patients presenting with advanced disease and hCG levels $>10^5$IU/l, the decay curve of the fall in the log of the hCG concentration is not linear. In a number of these patients the hCG appeared to plateau around 20 IU/l and subsequently gradually reached the normal range (<5 IU/l). It is possible that in some of these patients the addition of cis-platinum to the chemotherapy had little influence on the outcome since with more experience of this phenomenon a number of patients who continued on the EMA/CO regimen achieved complete remission despite this biphasic decay in the hCG concentrations. Therefore the contribution of cis-platinum to the survival of these patients is probably less than it appears from Table 6.

Once drug resistance has developed in patients with high risk GTT, salvage surgery is important. The principal sites for surgery in these patients are pelvis, lungs and brain. The results of surgery are shown in Tables 6 and 7. The problem of identifying residual sites of active disease is clearly shown by the fact that not all persisting radiological abnormalities contained viable tumour. This is particularly so of hysterectomy specimens where only 15% of patients had a major benefit from hysterectomy. The clinical usefulness of thoracotomy and craniotomy was clearly higher (Table 7).

There are two principal causes of death in these patients. There is a group of early deaths from patients presenting with very advanced disease who died within a matter of days, mainly from respiratory failure with widespread pulmonary replacement by tumour or from CNS damage (Table 2). The second group of patients who died in the series died mainly from drug resistance (two in the no prior treatment group and six in the prior treatment group). Two patients died in the postoperative period from intrathoracic haemorrhage following thoracotomy. One patient, who died from acute myeloid leukaemia, was treated with EMA/CO chemotherapy for a total of 9 months (a total of 30 weekly treatments including 8·4 g/m^2 cyclophosphamide). Her leukaemia is regarded as therapy-induced and emphasizes the need for limiting the duration of chemotherapy in order to minimize this particular complication of cytotoxic chemotherapy.

The toxicity from EMA/CO chemotherapy in this group of patients is essentially the same as that reported by Newlands *et al.* (1986). The main dose-limiting toxicity was leucopenia, followed by thrombocytopenia. Approximately 40% of patients required transfusion during chemotherapy.

Discussion

A number of other chemotherapeutic regimens had previously been used in patients with high risk GTT We have previously reported our results using the CHAMOCA regimen which gave a survival of 76% (Bagshawe & Begent 1981). However, the CHAMOCA schedule induced cumulative myelotoxicity and did not entirely overcome the problem of drug resistance. A randomized trial comparing MAC

Table 7. Histological and clinical assessment of salvage surgery after failure to achieve complete remission on EMA/CO (all patients %)

	Number
Hysterectomy	13
Histology positive	4 (31)
Major benefit*	2 (15)
Thoracotomy	14
Histology positive	12 (86)
Major benefit	6 (43)
Craniotomy	7
Histology positive	6 (86)†
Major benefit	5 (71)

* Major benefit: Clearcut fall in hCG following surgery allowing complete but not necessarily long term remission to be achieved with additional post operative chemotherapy.

† Patient with negative histology for choriocarcinoma had cerebral toxoplasmosis

Six patients had more than one operation

(methotrexate, actinomycin D and chlorambucil) chemotherapy with a modification of CHAMOCA (CHAMOMA) was reported by Curry *et al* (1989). When CHAMOMA chemotherapy is given as in this study, with long delays because of myelosuppression, the results are relatively poor and no better than with MAC chemotherapy. A further modification of the CHAMOCA protocol was used by Weed *et al.* (1982) who obtained complete remission in only 10 of 18 patients (58%). Better results were achieved using the CHAMOMA schedule by Wong *et al.* (1986) who obtained complete remission in 41 of 50 patients (82%). Cis-platinum is also an active agent in GTT (Newlands 1982). There have been several reports using the combination of cis-platinum and vinblastine and bleomycin in GTT. Schlaerth *et al.* (1980) reported two sustained remissions. Hainsworth *et al.* (1983) reported a further two complete remissions with this combination. Gordon *et al.* (1986) reported a larger series of 11 patients who had failed on MAC chemotherapy and sustained remissions were obtained in only two patients. Two further reports of this combination obtained sustained remissions in four of seven (DuBeshter *et al.* 1989) and five of eight patients (Azab *et al.* 1989). Significant activity of cis-platinum combinations produced sustained remissions in 19 (86%) in a group of 22 patients (Theodore *et al.* 1989).

GTTs can occur after any form of pregnancy. Where a patient has the commonest antecedent to a GTT, a hydatidiform mole, with the UK registration scheme and serial hCG estimations, very few of these patients should reach the high risk group (Table 1). During this period (1979–1989) 6545 patients were registered for hydatidiform mole follow-up and 501 (7.6%) required chemotherapy. Only 12 (0.2%) of these patients required EMA/CO chemotherapy. The reasons for these patients being high risk were: (i) early post mole high risk disease in three (hCG $>10^5$IU/l and/or multiple metastases); (ii) defaulted follow-up in four; (iii) correct follow-up to 2 years but late relapse in three (one after a subsequent term pregnancy); (iv) late registration in two patients. The principal risk factors in this group were: interval from antecedent pregnancy >12 months in seven; hCG persistently $>10^5$ IU/l post evacuation in two; multiple metastases in three.

The heterogeneity of the patient population is emphasized by the early deaths in Table 2. None of these 10 patients had an antecedent molar pregnancy. Since a GTT following a full-term delivery can grow very rapidly, it is not possible for all patients to be diagnosed at an early stage in their disease. Overall a GTT following a full-term delivery is uncommon, occurring in approximately 1 in 50 000 deliveries but these patients account for just under 13% of those treated at the Charing Cross Hospital. Widespread pulmonary metastases present the commonest problem in these patients and, despite a rapid response in terms of a fall in hCG to chemotherapy, further deterioration in pulmonary function can occur. Mechanical ventilation in these patients should be avoided since none of our patients in whom this has been used has survived. We have devised criteria which predict early respiratory death with 100% sensitivity and 38% positive predictive value (Kelly *et al.* 1990). Potentially the use of extra-corporeal membrane oxygenation (ECMO) might allow some of these patients to be salvaged although the anti-coagulation required for this procedure in a patient with widespread haemorrhagic tumour clearly carries a substantial risk.

The second most common cause of death in these patients is cerebral oedema from widespread cerebral metastases. If multiple, these metastases clearly will continue to present a problem in management but if isolated, our policy has moved progressively towards surgical removal of the metastasis at the start of treatment (Rustin *et al.* 1989). It is the early deaths that make the survival in patients who have received no prior treatment worse (82%) than survival in patients who had received prior chemotherapy (89%).

The pattern of deaths after the failure of chemotherapy are more typical of treatment failures with chemotherapy in other less chemosensitive tumours. The commonest cause of death here is drug resistance, accounting for 8 (73%) out of 11 deaths. Two patients died of arterial haemorrhage shortly following a theracotomy attempting to remove large intrathoracic metastases. One patient died of a therapy-related complication, acute myeloid leukaemia, which is related to both dose and duration of treatment.

With a decade's experience of using EMA/CO chemotherapy in patients with high risk GTT, the survival is clearly good and the toxicity of this schedule is predictable and the long term complications are rare. At present we would regard this schedule as the treatment of choice for these patients. So far we have preferred to keep cis-platinum, the main active agent not included in the EMA/CO schedule, in reserve for patients whose tumours develop drug resistance. It is possible that the results might be further improved by integrating cis-platinum into the initial therapy of these patients in a schedule such as EP/EMA. This approach is now more feasible with the introduction of the 5HT3 antagonists as more effective antiemetics (such as ondansetron, either alone or with the addition of dexamethasone (Smith *et al.* 1990)). In patients receiving prolonged chemotherapy with EP/EMA, the dose-limiting toxicity becomes primarily peripheral neuropathy, with renal toxicity being less prominent at this dose of cis-platinum. However, an alternating schedule using a nephrotoxic drug with the dominantly renally excreted methotrexate is a regimen with inherent lethal toxicity. It is certainly not to be recommended except in a specialist centre fully equipped to monitor renal function and, in selected cases, methotrexate concentrations.

Salvage treatment after failure to achieve complete remission on EMA/CO is still successful in most of these patients. Either with the introduction of cis-platinum into the EP/EMA schedule or with the addition of surgery, 30 (77%) of 39 patients have achieved sustained remissions (Table 6). Curiously, the primary site of the tumour in the uterus has a relatively low yield following chemotherapy in terms of removal of active tumour and of obtaining clinical benefit. Only 2 (15%) of 13 patients having a hysterectomy clearly benefited from this procedure. In contrast, 43% of those patients having a thoracotomy and 71% of those patients having a craniotomy clearly benefited from these surgical procedures. In a number of these patients there are multiple radiological abnormalities still present at the end of chemotherapy and the selection of the anatomical site for surgery can be helped by radioimmunolocalization with anti-hCG scanning (Begent *et al.* 1987). Even on relapse, the salvage rate with further therapy is still reasonable and 6 (75%) of 8 patients relapsing after EMA/CO therapy have achieved a further sustained remission.

The toxicity with the EMA/CO schedule is predictable and manageable. Apart from the single patient who developed acute myeloid leukaemia, long-term sequelae have been remarkably few. The majority of patients re-establish regular menstruation within 2–6 months after completing therapy. A number of these patients have subsequently had successful pregnancies, although a detailed analysis of the outcome of these has not yet been performed. It may be possible to increase the dose intensity of the EMA/CO schedule still further with the addition of the haemopoietic growth factors G-CSF or GM-CSF which may reduce the proportion of patients developing drug resistance.

Some of these patients with apparent GTTs may have non-gestational tumours with trophoblastic differentiation. This may account for some of those who develop drug resistance. If this is so, then the true survival of the patients with gestational tumours is even higher than is apparent from these results. Included in this series is a patient who has had her tumour analysed with locus specific mini satellite probes to identify restriction fragment length polymorphisms in the DNA of her tumour, the patient and her partner (Fisher *et al.* 1991). Although her initial hCG was $>1\times10^6$ IU/l (which is unusually high for tumours of non-gestational origin), analysis of her tumour showed no evidence of paternal genes in the tumour. The presumed final diagnosis in this patient is of trophoblastic differentiation in a non-gestational tumour, probably bronchial in origin. This patient responded initially to chemotherapy, developed drug resistance and died of intrathoracic haemorrhage following a thoracotomy but had clearcut evidence of active disease at this time.

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Menstrual symptoms in women with pelvic endometriosis

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Abstract

Objective—To investigate menstrual symptoms in relation to pelvic pathology.
Design—A prospective questionnaire-based study.
Setting—Aberdeen Royal Infirmary, Scotland.
Subjects—1250 questionnaires were sent out prior to planned admission and 1200 women (96%) brought the completed questionnaires. They comprised 598 women undergoing laparoscopic sterilization, 312 having laparoscopy because of infertility, 156 having laparoscopy because of chronic pelvic pain and 134 women undergoing abdominal hysterectomy for dysfunctional uterine bleeding.
Main outcome measures—The occurrence of dysmenorrhoea, menorrhagia, menstrual regularity, premenstrual spotting, deep dyspareunia and pelvic pain in women with either endometriosis and post infective pelvic adhesions or a normal pelvis.
Results—Menorrhagia, menstrual irregularity and premenstrual spotting occurred with equal frequency in all groups. Deep dyspareunia, pain after intercourse and recurrent pain unrelated to menstruation or coitus was more common in women with endometriosis and those with post infective pelvic adhesions than in those with a normal pelvis. Dysmenorrhoea appears to be more prevalent among women having endometriosis.
Conclusions—Menstrual symptoms, while raising a high index of suspicion for endometriosis, are not entirely reliable as indicators of disease. Dysmenorrhoea is the most common reported symptom in endometriosis sufferers. Diagnostic laparoscopy should be considered before institution of treatment in women complaining of pelvic pain and menstrual symptoms.

Endometriosis accounts for the second largest category of gynaecological publications (Kempers 1985). Despite this, our knowledge of many aspects of the disease is incomplete and this includes symptomatology. Patients who have extensive disease may have no symptoms, whereas patients with only minimal involvement may complain of disabling dysmenorrhoea. Associated symptoms include pelvic pain, rectal pain, dyspareunia and abnormal vaginal bleeding (Buttram 1979a, b; Puolakka *et al.* 1980; Ranney 1980).

Pelvic pain and dyspareunia among patients with endometriosis can occur when the peritoneal lesion becomes firmly bound within a fibrotic wall and maintains its functional activity each month, so that the unyielding scar tissue causes increased tension and pain. However Roddick *et al.* (1960) demonstrated that hormonally responsive ectopic endometrium was not a prerequisite for painful symptoms. Other possible causes of pain include fixed uterine retroversion, tender uterosacral nodules (Hammond & Haney 1978) and possibly increased peritoneal fluid vol-

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umes and prostaglandin content (Kauppilla *et al.* 1984; Dinarello, 1985). However, it is also known that up to 50% of women with pelvic pain will have no demonstrable pathology (Beard *et al.* 1977).

Abnormal uterine bleeding occurs in 11—34% of women with endometriosis and may present as oligomenorrhoea, polymenorrhoea, menorrhagia, post-coital spotting or premenstrual spotting (Stevenson & Campbell 1960; Wentz 1980). Muse & Wilson (1982) suggested that abnormal uterine bleeding may be a reflection of ovulation dysfunction.

Similarly, congestive dysmenorrhea occurs in 25—90% of women with endometriosis (Goldstein *et al.* 1980; Chatman & Ward 1982) and it has been suggested that retrograde menstruation may be the cause (Huffman 1981; Telinde & Scott 1950). On the other hand, Blumen krantz *et al.* (1981) reported nine women undergoing peritoneal dialysis where retrograde menstruation was observed but none of these complained of dysmenorrhoea. In two studies involving laparoscopy during menstruation (Reti *et al.* 1983; Liu & Hitchcock 1986) the occurrence of dsymenorrhoea was not significantly different whether patients had retrograde menstruation or not. Similarly, dysmenorrhoea is a relatively common symptom in the general population ranging from 5% to 62% (Sobczyk 1980).

Many of the above reports consist of retrospective studies and lack suitable controls. The purpose of this prospective questionnaire-based study was to examine menstrual symptoms in relation to a finding of endometriosis in a large group of women of reproductive age.

Patients and methods

A total of 1250 questionnaires were sent to patients attending Aberdeen Royal Infirmary who were to have laparoscopy for sterilization, infertility, chronic abdominal, or pelvic pain, or abdominal hysterectomy for dysfunctional uterine bleeding. All were asked to complete the questionnaire before their admission to hospital. Of these, 1200 (96%) patients brought completed questionnaires on arrival at hospital. Of the remaining women, 35 refused to complete the questionnaire and 15 brought incomplete questionnaires and were excluded from the analysis. None of these 50 patients had pelvic endometriosis diagnosed subsequently. The study group of 1200 patients included 598 women undergoing laparoscopic sterilization, 312 having laparoscopy for infertility, 156 having laparoscopy because of pain, and 134 undergoing abdominal hysterectomy. They were asked about their age and menstrual pattern at the menarche, current menstrual history, deep dyspareunia and its effect on sexual life, and pelvic pain.

All laparoscopies were performed under general anaesthesia with endotracheal intubation. A 10 mm end viewing laparoscope was introduced through an infra-umbilical incision, a modified Palmer-Jacob's forceps introduced suprapubically for manipulation and the pelvis was inspected systemically. The uterus was held in acute retroversion and its anterior surface, utero-vesicle reflection and all the peritoneal surfaces as far as the insertion of round ligaments laterally and the anterior surface of the broad ligament were inspected. Then, with the uterus in acute anteversion, the posterior surface of the uterus, uterosacral ligaments, pouch of Douglas and rectovaginal septum were inspected, and free fluid from that area was aspirated. The posterior leaf of the broad ligament was also inspected on both sides. Both Fallopian tubes were inspected along their entire length: their mobility, presence of peritubal adhesions or tubal distortion and functional relation of fimbria to the ovaries were noted. Both ovaries were mobilized to detect endometriosis on the under surface and for periovarian adhesions. The diagnosis of endometriosis was based on the characteristic visual appearances of the disease and biopsies were not taken. All endometriotic deposits were recorded on a preprinted drawing of pelvic organs for each patient and the extent of endometriosis was scored using the revised American Fertility Society (AFS) Classification (American Fertility Society 1985). In this system a score <5 signifies minimal endometriosis, 6–15 mild endometriosis, 16–40 moderate endometriosis and a score of >40 indicates severe endometriosis.

Among infertile patients, tubal patency was confirmed by the transcervical injection of 0·5% methylene blue dye in isotonic saline using a Leach Wilkinson cannula. Patients undergoing laparoscopic sterilization had Filshie clips applied to the isthmic part of the tubes. Among those undergoing abdominal hysterectomy, only endometriotic deposits noted at the time of operation were recorded on the data sheet; his-

Table 1. Pelvic findings in the study groups

Study group	Endometriosis n (%)	Pelvic adhesions n(%)	Normal pelvis n(%)	Total n
Laparoscopic sterilization	37 (6)	129 (22)	432 (72)	598 (100)
Infertility group	107 (35)	78 (25)	127 (40)	312 (100)
Chronic abdominal pain	24 (15)	43 (28)	89 (51)	156 (100)
Abdominal hysterectomy for dysfunctional uterine bleeding	33 (25)	28 (21)	73 (54)	134 (100)
Total	201 (17)	278 (23)	721 (60)	1200 (100)

tologically proven lesions (i.e., adenomyosis or other focal microscopic deposits in the histology specimen) were not considered in the data analysis.

The laparoscopies were performed by six and the hysterectomies by three experienced surgeons. On each occasion, the operators performed the procedures according to the study protocol and recorded their findings on a preprinted sheet.

Statistical analysis

Data were analysed using the Statistical Package for the Social Sciences (SPSS-X) on a mainframe computer (University of Aberdeen).

Results

Of the 1200 women, 201 (17%) had endometriosis. In 278 (23%) there were pelvic adhesions without evidence of endometriosis and these were assumed to be post-infective. In the remaining 721 (60%) the pelvic organs appeared normal (Table 1). Most of the 201 patients with endometriosis had mild disease ($n = 146$, 73%) and the others had moderate ($n = 46$, 23%) or severe ($n = 9$, 4%) disease. The mean age at menarche was 12·84 (SD 1·53) years in the endometriosis group, 13·23 (SD 1·50) in women with pelvic adhesions and 13·0 (SD 1·50) years in women with normal pelvis ($f = 1{\cdot}208$; df 2; $P<0{\cdot}025$).

Menstrual symptoms

A greater proportion of women in the endometriosis group complained of dysmenorrhoea compared with those who had pelvic adhesions ($\chi^2 = 11{\cdot}00$; $P<0{\cdot}001$) and those with a normal pelvis ($\chi^2 = 21{\cdot}6$; $P<0{\cdot}001$). A greater proportion of the group with endometriosis and the group with pelvic adhesions had irregular periods, compared with those who had a normal pelvis ($\chi^2 = 9{\cdot}91$; $P<0{\cdot}02$). There was no difference between the groups in relation to subjective assessment of menorrhagia or premenstrual spotting (Table 2).

The two asymptomatic groups, the women having sterilization or infertility investigations, were then studied separately. Again there did not appear to be a greater frequency of menorrhagia or premenstrual spotting in the women with endometriosis (Table 3).

Pelvic pain

Patients with endometriosis and pelvic adhe-

Table 2. A comparison of menstrual symptoms in women with and without endometriosis ($n = 1200$)

Variables	Endometriosis (n = 201)		Pelvic adhesions (n = 278)		Normal pelvis (n = 721)		Significance with 2 df	
							χ^2	P
	n	(%)	n	(%)	n	(%)		
Dysmenorrhoea	137	(68)	140	(50)	358	(50)	24·48	<0·001
Present periods regular	154	(77)	206	(74)	632	(88)	9·92	<0·02
Menorrhagia	110	(55)	125	(45)	365	(51)	4·89	>0·05
Premenstrual spotting	56	(30)	79	(28)	190	(26)	2·28	>0·05
Deep dyspareunia	75	(37)	93	(33)	168	(23)	25·64	<0·001
Pain after intercourse	29	(14)	42	(15)	72	(10)	6·41	<0·05
Pelvic pain	118	(59)	165	(59)	346	(48)	17·95	<0·001

Table 3. A comparison of menstrual symptoms in women having laparoscopy for sterilization or infertility according to the occurrence of endometriosis or pelvic adhesions

Variables	Endometriosis ($n = 144$)		Pelvic adhesions ($n = 207$)		Normal pelvis ($n = 559$)		Significance with 2 df	
							χ^2	P
	n	(%)	n	(%)	n	(%)		
Dysmenorrhoea	88	(61)	82	(40)	232	(41)	20·194	<0·001
Present periods regular	127	(88)	169	(82)	537	(96)	4 87	>0·05
Menorrhagia	64	(44)	73	(35)	231	(41)	3·44	>0·05
Premenstrual spotting	31	(21)	52	(25)	119	(21)	4·54	>0·05
Deep dyspareunia	43	(30)	46	(22)	91	(16)	14·30	<0·001
Pain after intercourse	16	(11)	20	(10)	25	(4)	11·83	<0·001
Pelvic pain	76	(53)	99	(48)	216	(39)	11·91	<0·005

sions complained of both deep dyspareunia and pain after intercourse significantly more frequently than women with a normal pelvis. Similarly recurrent pelvic or abdominal pain unrelated to menstruation or coitus was more common in both groups with pathology (Table 2). There was no difference in the pain symptomatology when the symptomatic women (i.e., laparoscopy for pain and hysterectomy groups) were excluded (Table 3).

Symptoms in relation to severity of endometriosis were compared in three subgroups of women with endometriosis; mild, moderate and severe endometriosis. There was no relation between symptomatology and the severity of endometriosis (Table 4).

Discussion

This large prospective questionnaire-based study has shown that women with endometriosis experience dysmenorrhoea more often than those with a normal pelvis or with evidence of previous pelvic infection. This study fails to confirm an earlier observation (Ranney 1980) that minimal-mild endometriosis causes severe dysmenorrhoea because the occurrence of dysmenorrhoea was not influenced by the severity of the disease.

Deep dyspareunia and pelvic pain were both noted in an equal proportion of patients with endometriosis and with pelvic adhesions and more commonly than among those with a normal pelvis. These symptoms may be related to several potential causes, such as fixed ovaries, scarring or retraction of peritoneal surface, and reduced uterine mobility (Roddick *et al.* 1960; Hayden & Soderstrom 1977) and these may be the common mechanisms in women with pelvic adhesions or moderate to severe endometriosis. However, this would be harder to explain in the group with mild endometriosis.

The greater frequency of dysmenorrhoea in women with endometriosis than in those with pelvic adhesions is worthy of comment. The original concept of Sturgis & Call (1954) that fibrosis and scarring may be a causative factor may not be true. Several possible mechanisms

Table 4. A comparison of menstrual symptoms in women with endometriosis according to the severity of endometriosis

Variables	Degree of endometriosis						Significance with 2 df	
	Mild ($n = 146$)		Moderate ($n = 46$)		Severe ($n = 9$)		χ^2 df	P
	n	(%)	n	(%)	n	(%)		
Dysmenorrhoea	102	(70)	31	(67)	4	(44)	1·92	>0·05
Present periods regular	111	(76)	34	(74)	9	(100)	2·546	>0 05
Menorrhagia	85	(58)	21	(46)	4	(44)	2·33	>0·05
Premenstrual spotting	41	(28)	13	(28)	2	(22)	0·274	>0·05
Deep dyspareunia	51	(35)	19	(41)	5	(55)	2·293	>0·05
Pain after intercourse	20	(14)	8	(17)	1	(11)	0·778	>0·05
Pelvic pain	82	(56)	31	(67)	5	(55)	2·705	>0·05

have been put forward to explain dysmenorrhoea, deep dyspareunia and pelvic pain in women with endometriosis. It has been suggested that the endometrium of women with endometriosis produces higher levels of prostaglandins (Willman *et al.* 1976). Furthermore, endometriotic implants are capable of producing prostaglandins *in vitro* (Ylikorkala & Viinikka 1983; Moon *et al.* 1981) and increased amounts of peritoneal fluid with increased prostanoid content have been observed in association with endometriosis (Dawood *et al.* 1984; Badawy *et al.* 1982).

However, a recent exhaustive review of the literature suggests that data on increased peritoneal fluid volumes and prostaglandin content are inconsistent (Mahmood & Templeton 1990). Furthermore if endometriosis implants do secrete prostaglandins, then their treatment should alter the symptoms. Lim *et al.* (1989) used electrocautery to ablate all the visible endometriotic implants at laparoscopy but 3 months later the frequency and severity of dysmenorrhoea remained unchanged. Similarly, medical treatment with danazol (Barbieri *et al.* 1982; Buttram *et al.* 1982; Ronnberg & Jarvinen 1984) and medroxyprogesterone acetate (Telimaa *et al.* 1987) can alleviate symptoms in from 62 to 87% patients but there is a high recurrence rate of up to 38% (Puleo & Hammond 1983). Pelvic adhesions associated with endometriosis do not respond to medical treatment (Barbieri *et al.* 1982) and it is relevant that about a third of women without obvious pathology also complain of menstrual symptoms. Therefore, factors other than endometriosis and pelvic adhesions may be involved in causing dysmenorrhoea, pelvic pain and deep dyspareunia (Beard *et al.* 1977).

Hypercontractility of the uterus has been proposed (Mäkarainen 1988), a problem that is not abolished by treatment with danazol or prostaglandin synthesis inhibitors.

In conclusion, dysmenorrhoea appears to be more prevalent in women with endometriosis. Deep dyspareunia and pelvic pain were noted with equal frequency in women with pelvic pathology, regardless of whether endometriotic or post-infective in nature.

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Experience with tissue expansion vaginoplasty

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Summary. In vaginal agenesis, a vagina can be treated by tissue expansion vaginoplasty. We have performed 17 such procedures. One procedure was abandoned because of infection of the temporary implant. In four women the first stage had to be repeated: in one the implant was placed too superficially, in another it did not provide adequate expansion, in a further instance the implant became infected and the fourth woman received a surgical wound to her labia. The second stage was successful in all 16 women who now have a vagina lined with viable epithelium. The vaginal length was satisfactory in all but one. Two women complained of a vaginal discharge due to hair at the vaginal vault, two women developed postoperative haematomas and one experienced introital stenosis. The disadvantage of the procedure is that it requires two operative stages and involves a prolonged hospital stay but it is not technically complex and results in a full length vagina that does not require dilatation.

Surgeons often say that if there is more than one operation for a condition then the ideal procedure does not exist. Many ingenious operations for vaginal agenesis have been described. These include the creation of a perineal pouch from labia minora and the construction of a recto-vaginal cavity lined with amnion, rabbit bowel, split skin, full thickness skin flaps, pedicle grafts or even free bowel grafts (Johnson & Lilford, 1990). Lilford *et al* (1988) reported a new surgical procedure, namely, tissue expansion vaginoplasty. We report the results of 17 women managed with this technique.

Patients and methods

In the last 3 years we have abandoned amnion-graft vaginoplasty and have attempted tissue expansion vaginoplasty in 17 women. One woman's vagina had been obliterated by previous surgery and the rest had congenital malformations of their vagina. Two women had haematometra and haematocolpos of a short upper vagina, one had complete vaginal and cervical agenesis with haematometra, one had agenesis of the lower half of her vagina but had a thin fistulous tract to the exterior and the remaining patients had agenesis of vagina and uterus (classical Rokitansky syndrome). One woman in the latter group had had a William's operation when she was 18 but the pouch was small and coitus was painful. All women had a normal female karyotype and had undergone normal puberty. One patient had a single kidney, one had Klippel Feil syndrome and two had bony defects of the lower spine.

Procedure

Lilford *et al.* (1988) described details of the sur-

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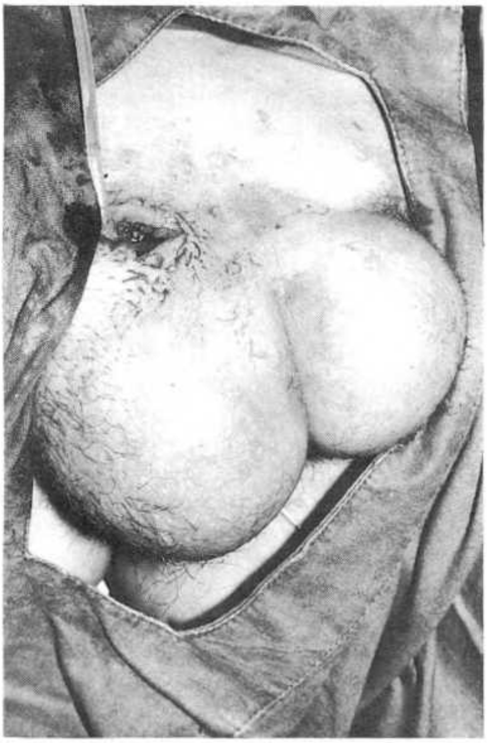

Fig. 1. Tissue expanders stretching the skin in the perinium.

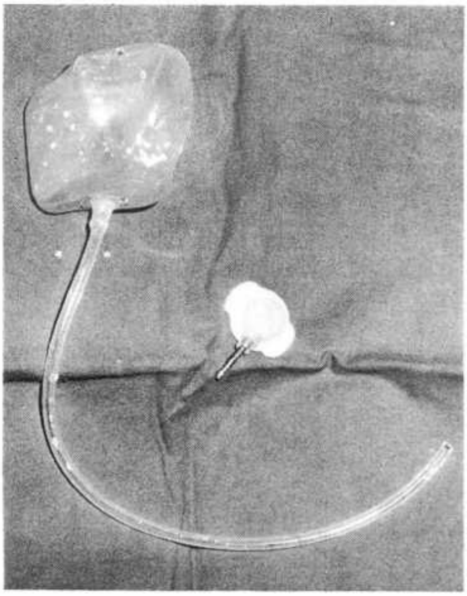

Fig. 2. Commercially available tissue expander. (100 or 75 ml rectangular expander, Medasil, Leeds; Batchelor, 1990).

gical procedure in reporting the first case in this series. The operation involves expanding the labia minora into pseudoscrota (Fig. 1), using tissue expanders, and this extra skin is used to line a rectovesical cavity. Careful counselling is essential and more recently patients have been visited by a woman who has undergone the procedure.

The first stage of the procedure involved placing subcutaneous tissue expanders (Fig. 2) underneath and slightly medial to each labium minus. These expansile balloons were inserted through bilateral groin icisions and were positioned by tunnelling them underneath the skin. The woman expanded each balloon gradually by adding up to 5 ml of normal saline each day. The labia must be checked for chafing, ischaemia and infection. Initially this was done as an out-patient procedure, but walking soon became difficult and we now keep patients in hospital. Once each expander contained approximately 80 ml (3-5 weeks) the second stage of the procedure was performed under general anaesthesia. The balloons were removed after disrupting the pseudocapsule by further balloon expansion and the extra skin created by the expanded labia minora was used to make skin flaps (Fig. 3). Where possible, the flaps were created from the non-hair-bearing skin on the inside of the labia minora. A rectovesical cavity was created by blunt dissection and lined by these flaps which were fashioned into a pouch with a posterior vascular base. The closed end of the pouch was sutured to the Mullerian remnants via a laparotomy in the 12 patients with Rokitansky syndrome. In the patients with haematocolpos the top of the pouch was left open and the skin flaps were sutured to the upper vagina. This involved dissecting the haematocolpos off the rectum and incising it posteriorly to create a long anterior upper flap. Menstrual blood was allowed to drain and this flap was sutured to the lower skin flaps to create a non-annular anastomosis. In women with haematometra and cervical agenesis the perineal skin flaps were sutured to the inside of the uterus. To guide this difficult dissection, the uterus was opened via a laparotomy. A Foley catheter in the uterus stented the anastomosis and was retained in position for 10 days.

Two closed suction drainage systems were used in all patients and the bladder was drained with a suprapubic catheter. The procedure created a long vagina lined with full thickness skin on a vascular pedicle.

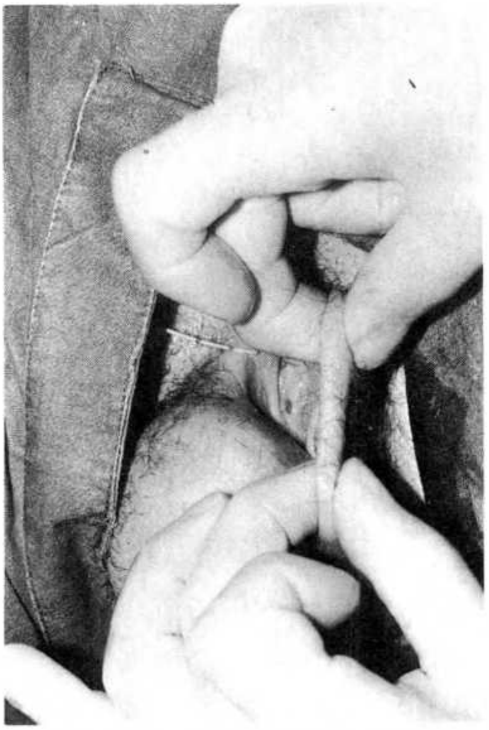

Fig. 3. Once the expander is removed there is a considerable amount of extra skin.

Results

During the inflation phase walking became difficult for all women who had to waddle as if they were saddle sore and several found this embarrassing. The entire expansion and the stay in hospital lasted between 4 and 7 weeks. Early in the series, the tissue expanders became infected in two women. On days 32 and 39 respectively the skin overlying each expander became red, tender and indurated and the expanders were removed. The vaginoplasty was abandoned in one of these women and she is now attempting non-surgical enlargement of the vagina. In the other, the expanders were inserted again after 6 months and it then became possible to proceed to the second stage. The skin over an expander became red and tender in a further woman but this resolved within a week. In one other woman the labium was fenestrated as the tissue expander was inserted and the first stage was postponed and repeated later. Early in the series the expanders needed to be resited in two women, in one because they were placed too superficially and began to ulcerate and in the other because they were placed too deep and laterally and did not provide enough tissue expansion (Table 1). In the other 11 women there were no complications. A flow chart of the management and results in the 17 women is shown in Fig. 5.

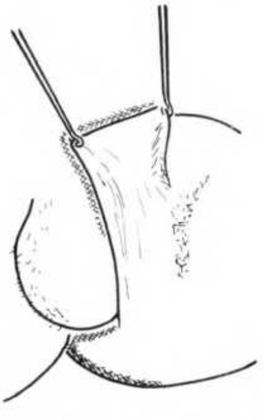

Fig. 4. The extra skin created by expanding the labia minora is used to make the skin flaps that will line the recto-vesical cavity.

The second operation was uneventful in all 16 women. Four women required intra-operative blood transfusion (not more than 4 units) and the greatest haemoglobin drop was 5 g/dl. In one patient blood loss was due to a vulval haematoma that required evacuation and in another, venous blood continued to ooze into the drains postoperatively from the neovagina. Other than postoperative pyrexia on days 1–2 after surgery, there were no other complications attributable to surgery. Initially women stayed in hospital for 2 weeks after the second operation; this has subsequently been reduced to 10 days. At the beginning of the series the women were examined again under general anaesthesia 1 month after the operation. The wound and the skin lining the vagina always appeared healthy. All the women were seen 6 weeks after operation and all were asymptomatic and well. The new vagina admitted at least one finger to the vault in all women. The shortest vagina reached 6 cm and the remaining patients have vaginas of 9–10 cm. At least four women have begun intercourse and they claim to reach orgasm during intercourse. All were warned to use the lubrication in anticipation of Bartholin's gland failure but one no longer finds this necessary. One woman complained of introital stenosis and although we had planned a small Z plasty at the introitous, the superficial dyspareunia resolved spontaneously within 3 weeks. Two women complained of a white/yellow discharge that stained their pants.

Table 1. Outcome in 17 women treated with a Lilford vaginoplasty

Patient no.	Age at surgery (years)	Pathology	Duration of complete procedure (days)	Transfusion requirement (units	Complications
1	14	Haematometra	34	2	None—now menstruating
2	17	Rokitansky syndrome	30	0	None
3	22	Rokitansky syndrome	79	0	Left balloon too superficial, began to ulcerate and required resiting. Hair at the vaginal vault requiring elecrolysis
4	20	Rokitansky syndrome	55	0	None
5	17	Rokitansky syndrome	31	0	Expanders needed resiting
6	16	Rokitansky syndrome	16	0	Infection Procedure abandoned
7	19	Rokitansky syndrome	29	0	Post coital spotting due to vault granulation tissue
8	16	Rokitansky syndrome	35	0	Infection of tissue expander treated with antibiotics
9	17	Hydrocolpos	30	4	Vulval haematoma 1 day after 2nd stage vaginoplasty (resolved spontaneously)
10	56	Iatrogenic	18	0	None
11	18	Haematometra	40	0	None—now menstruating
12	19	Rokitansky syndrome	50	4	Right balloon was infected by *Staphylococcus aureus* and needed resiting. Left vulval haematoma, superficial dysparunia, stitch sinus in the groin and vaginal discharge from hair at the vaginal vault
13	37	Lower vaginal agenesis	30	0	None
14	41	Rokitansky syndrome (Williams operation at the age of 18)	31	0	Labia damaged during insertion of expanders and the first stage was repeated
15	17	Rokitansky syndrome	24	0	Urinary tract infection Vaginal length only 6 cm
16	18	Rokitansky syndrome	35	0	None
17	18	Rokitansky syndrome	37	2	None

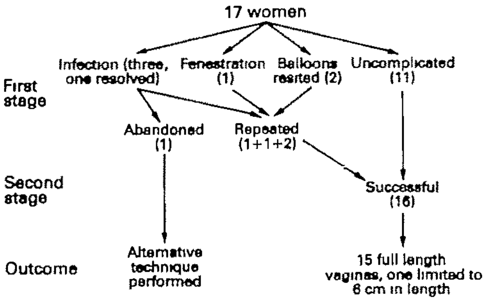

Fig. 5. Tissue expansion vaginoplasty, flow chart of management and results.

This was due to a patch of hair from the skin flap that had been transposed to the vault of the neovagina. These hair follicles were removed by electrolysis under general anaesthetic and although this has had to be repeated, it has relieved symptoms. This complication occurred early in the series and we are now careful to avoid the use of skin containing large numbers of hair follicles.

Finally, one woman developed a small sinus in her groin some weeks after the second procedure. A nylon suture was removed under local anaesthesia and the sinus healed.

Discussion

There are two major problems with this vaginoplasty; infection and prolonged hospitalization. The perineum is a highly contaminated environment and tissue expanders may become infected and require removal. Infection occurred in the early phase of our series, implying that this was related to our inexperience, but we still quote an infection risk of at least 10% to our patients. Secondly, a hospital stay of nearly 2 months is an unwelcome intrusion into a teenager's life and requires considerable emotional stamina.

Other theoretical complications are shared with most other techniques and include damage to the rectum and bladder and venous haemorrhage from the rectovesical space. Discharge secondary to hair follicles in the vaginal vault represent a further, but minor, disadvantage and we believe we can now avoid this complication by using only non or sparsely hair-bearing skin.

There are considerable advantages from tissue expansion vaginoplasty. The neovagina is in the correct axis and of good length. Because it is lined with full thickness epithelium on a pedicle flap it does not require dilatation and it will not contract or cicatrise. It has all the advantages of the free flap vaginoplasty and other pedicle flaps with a lower degree of technical difficulty. It leaves the woman with an unmutilated vulva and she does not have the problem of an introital stoma through which bowel may prolapse and she does not run the risk of AIDS from an amnion graft.

We now have experience with Williams's pouch (Williams 1964) and lining the rectovesical space with amnion (Dhall 1984), free flaps (Johnson *et al.* 1991), rectus abdominal flaps (Lilford *et al.* 1990) and vulval flaps based on the posterior labial artery (Wee & Joseph 1989). The latter is suitable for women with lower vaginal agenesis and very little introital hair but provided the women can withstand a period of uncomfortable hospitalization the tissue expansion vaginoplasty is our procedure of choice for most women.

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Crouching over the toilet seat: prevalence among British gynaecological outpatients and its effect upon micturition

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Summary. This study investigated whether British women prefer to crouch over public toilet seats, and measured the effect of such a voiding position on urine flow rate and residual urine volume. Of 528 consecutive women who attended a general gynaecological clinic and completed an anonymous questionnaire, 85% usually crouched over the toilet when using a public convenience, 12% applied paper to the seat and 2% sat directly on public toilet seats. When using a friend's bathroom 38% of the women voided by crouching. Results were similar for 155 patients attending a urodynamic clinic, 80 of whom were studied while voiding in both positions. There was a 21% reduction in average urine flow rate and a 149% increase in residual urine volume in the crouching position. Women undergoing urodynamic tests should be asked which voiding position they used before abnormal results are interpreted. Patients with a reduced functional bladder capacity may benefit from being encouraged to sit comfortably on the toilet whenever possible.

Anecdotal reports have suggested that many British women were taught by their mothers never to sit on the toilet seat in a strange bathroom. However, the extent to which this voiding position is used and its effect upon micturition have not been investigated previously.

The aims of the study were threefold; first to determine what percentage of women attending gynaecological outpatient departments usually void in the crouching position, second, to compare the prevalence of this voiding habit in women with urinary dysfunction, and third, to study whether urine flow rate and residual urine volume are affected by the crouching position.

Subjects and methods

Prevalence survey

Using an anonymous questionnaire, we surveyed 528 consecutive women (mean age 39·6, SD 14·1, range 11–81) attending general gynaecology clinics in Hull (425) and Liverpool (103).

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The questionnaire asked the patients' main reasons for attending the clinic, which were as follows: menstrual abnormality 25%, abnormal cervical smear 18%, abdominal pain 15%, infertility 13%, prolapse or incontinence 11%, contraception 3%, postoperative follow up 24%, other 18%, with 20% of patients circling more than one complaint. Parity was not recorded so as to avoid discussion of stillbirths and abortions.

For comparison we surveyed 155 consecutive women attending the Liverpool gynaecological urodynamic unit (mean age 47·8, SD 12·3, range 22–83) over a 4-month period.

Women were asked whether their mother had previously trained them not to sit down on toilet seats away from their own home, and whether they currently sat upon or crouched over public toilet seats. We also asked how women voided when using the toilet in a friend's house, and whether they preferred to apply paper to the seat before sitting down in either situation.

Study of micturition in sitting and crouching positions

Of the 155 women attending the urodynamic clinic, the first 80 consecutive patients (mean age 45·7, SD 13) who had a normal urinary flow rate in the sitting position were invited to undergo uroflowmetry and transvaginal ultrasound measurement of residual urine volume (Haylen 1989) for micturition in the crouching position. Average and maximum (peak) urine flow rates were measured. Because urine flow rate is known to be volume dependent, centile flow rates based on the volume of urine voided were derived from nomograms published by Haylen *et al.* (1989). These authors showed little variation in repeated urine flow rate measurements for the same patient; we recorded the order in which crouching and sitting micturition was performed so as to observe any test-order effect. Parity was recorded by the clinician for this study group.

Statistical analysis

The significance of changes in voiding variables for the two positions was determined using the paired Student's t-test. A pilot study of 14 patients gave an estimated mean difference in the main outcome measure (residual urine volume) of 30·5 ml (SD 32·4) for sitting versus crouching micturition: a sample size of 21 women would give a power of 99% at a significance level of 5%. As data were collected by non-invasive means, 80 patients with normal flow rates (defined as $>$ 10th centile on flow rate nomogram) were tested so as to allow analysis by each of four most common urodynamic diagnoses.

Results

Prevalence survey

Of the 528 general gynaecology patients, 85% said that they usually crouched over public toilet seats and only 2% sat directly on the public toilet without first covering it with paper. When asked about the use of a friend's bathroom, 37% said that they crouched over the toilet in this case. Women who used toilet paper to cover the seat tended to be older than those who preferred to crouch (Table 1).

When asked about training given by their mother, 70% remembered being instructed not to sit on public toilet seats. Of those who recalled

Table 1. Voiding preferences of 528 gynaecological outpatients and 155 women attending urodynamic clinic

	Public toilet				Friend's house			
Patient group	Crouch over seat		Place paper on seat		Crouch over seat		Place paper on seat	
	n (%)	Age (years) Mean (SD)	n (%)	Age (years) Mean (SD)	n (%)	Age (years) Mean (SD)	n (%)	Age (years) Mean (SD)
Urodynamic patients								
DI (n=73)	63 (86)	47 (13)	4 (5)	33 (3)	37 (51)	50 (13)	2 (3)	31 (5)
GSI (n=49)	39 (80)	47 (10)	2 (4)	56 (2)	16 (33)	48 (13)	1 (2)	59 –
Mixed GSI + DI (n=11)	11 (100)	49 (13)	– –	– –	6 (54)	48 (11)	– –	– –
Sensory urgency (n=17)	16 (94)	47 (12)	– –	– –	5 (29)	45 (11)	– –	– –
Normal bladder (n=5)	5 (100)	50 (12)	– –	– –	1 (20)	56 –	– –	– –
Gynaecological outpatients (n=528)	451 (85)	39 (14)	65 (12)	44 (15)	199 (38)	39 (14)	27 (5)	48 (16)

Abbreviations DI = detrusor instability, GSI = genuine stress incontinence

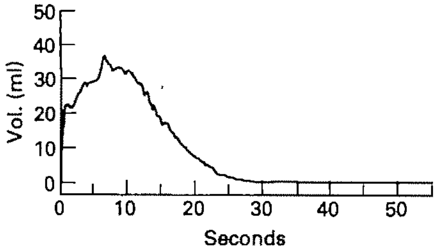

Fig. 1. Example of voiding variables for micturition in the sitting position. Maximum flow rate 37 ml/s; average flow rate 16 ml/s, voided volume 503 ml; maximum flow rate centile 40th; average flow rate centile 25th; residual urine 20 ml.

such training, 10% ignored this advice and usually sat down to void. Of the 156 women (30%) who had not been trained to avoid public toilet seats, 79% crouched over the seat regardless. The age of women who did recall such training (mean 38·7 years, SD 14) was no different from those who did not (38·8, SD 14). There were no significant differences between results for patients from Hull and Liverpool.

Survey of patients attending urodynamic clinic

In comparison with the women attending general gynaecology clinics, patients undergoing investigation for urinary dysfunction showed an equally strong tendency to crouch over the toilet seat (Table 1). However, the age trends regarding the use of paper on the seat varied between the diagnoses.

Patients with detrusor instability were more likely to crouch over the toilet at their friend's house (51%) than were patients with genuine stress incontinence (33%) ($\chi^2 = 4{\cdot}48$, $P < {\cdot}05$), but there were no obvious trends for other diagnostic groups. There were no significant differences in age for those who crouched or sat in either location, but women who crouched over public toilets tended to have had more children (2·6, SD 1·2) than women who sat down (1·5, SD 1·1) ($P = 0{\cdot}007$, 95% CI 0·3 to 1·8).

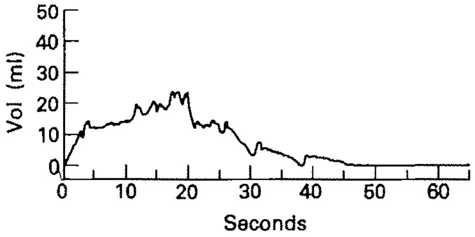

Fig. 2. Example of the same patient voiding in the crouching position Maximum flow rate 24 ml/s, average flow rate 10 ml/s; voided volume 466 ml; maximum flow rate centile 15th; average flow rate centile 3rd; residual urine 96 ml.

Urine flow rate and residual urine volume

Of the 80 women attending the urodynamic clinic who were studied in both voiding positions, 84% normally crouched over public toilets and 52% normally crouched over the seat in a friend's bathroom.

Typical examples of micturition in both positions are shown in Figures 1 and 2. When voiding in the crouching position, subjects produced a satisfactory peak flow rate but the average flow was reduced and micturition was often prolonged. As shown in Table 2 the mean of the average flow rates fell by 21% when patients crouched, and mean peak flow rate fell by 14%. Crouching micturition was associated with a mean increase in residual urine volume of 149%.

Comparison of the changes in flow rate and residual urine for patients with genuine stress incontinence (22), detrusor instability (41), mixed stress incontinence and detrusor instability (7), sensory urgency (8), and urodynamically normal bladder (2) showed no important differences between any of the diagnostic groups. The order in which the two positions was tested had no significant effect on residual urine volume (crouching first *vs.* sitting first $P > 0{\cdot}9$).

Using linear regression analysis, we found that neither age nor parity was significantly related to the changes in centile average flow rate or residual urine volume seen for micturition in the crouching position.

Discussion

The anonymous questionnaire showed that 85% of the 528 gynaecological outpatients surveyed in Hull and Liverpool do not usually sit on public toilet seats, and that this habit was almost equally strong in women who could not recall any maternal training about their voiding behaviour.

While gynaecological outpatients may not be typical of the female population as a whole, the wide range of ages and presenting complaints found in our sample showed that we studied a broad spectrum of women. After discovering the high rate of crouching micturition in the survey group, we have made enquiries of non-hospital attenders in various social settings which lead us

Table 2. Urine flow rates, centiles, and residual urine volumes for 80 women with normal micturition, voiding in the seated and crouched positions

	Sitting Mean (SD)	Crouching Mean (SD)	Mean change	95% CI	P value
Average flow rate (ml/s)	19·1 (10·5)	15·1 (7·7)	− 4·0	(−6·4, −1·6)	0·001
Average flow rate centile	41·0 (31·5)	33·0 (30·0)	− 8·0	(−15·4, −0·6)	0·035
Maximum flow rate (ml/s)	38·7 (14·8)	32·4 (15·5)	− 6·4	(−10·0, −2·7)	0·001
Maximum flow rate centile	50·6 (28·0)	44·8 (29·8)	− 5·9	(−12·0, 0·2)	0·057
Residual volume (ml)	19·9 (24·9)	49·7 (48·6)	+29·8	(19·0, 40·6)	0·0001

to suspect that a broad population survey would yield similar findings.

Discussion with the women before and during the study period revealed that many who refused to sit on public toilet seats regarded our urine flow rate equipment as a public facility; they were inclined to avoid sitting on it unless specifically asked to do so (which has now become routine practice in our unit).

We were surprised to find that 37% of the respondents would not sit on the toilet in a friend's bathroom, as this suggests an avoidance of toilet seats greater than might result from a desire for cleanliness. The strong tendency for women with detrusor instability to crouch over the toilet at their friend's house is difficult to account for but might suggest a preoccupation with toileting behaviour in such patients.

The observed reduction in flow rates and increase in residual urine volume might be explained in two ways. Firstly many subjects explained that they often did not remain in the awkward crouching position long enough to feel that all urine had been expelled. Secondly, Wennergren *et al.* (1989) found that children who voided whilst sitting on a high toilet seat with their legs and feet unsupported demonstrated increased electromyographic (EMG) activity in the pelvic floor muscles. They concluded that contraction of the adductor muscles was associated with failure of pelvic floor relaxation during micturition. Animal studies have also found that electrical stimulation of the hip adductor muscles produces inhibition of bladder contractility (Lindstrom & Sudsuang 1989). Voiding in the crouching position (as opposed to squatting) would involve tensing of the hip adductor muscles and may be associated with poor relaxation of the pelvic floor and urinary outflow tract.

The results of this study suggest that when low urinary flow rates or a high residual urine volume are encountered during urodynamic testing, the patient should be asked whether micturition took place in the sitting or crouching position. If the latter position was used then repeat studies with the patient sitting comfortably should be considered before accepting an abnormal test result as indicative of lower urinary tract dysfunction.

Patients with a reduced functional bladder capacity (such as those with detrusor instability or sensory urgency) may benefit from being encouraged to relax on the toilet seat and empty the bladder completely whenever possible. In view of the association between increased residual urine volume and urinary tract infection, it is possible that women predisposed to cystitis may also benefit from advice in this regard, although a specific study to substantiate this would be required.

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Oocyte and follicular fluid characteristics in women with mild endometriosis

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Summary. The follicular development, fertilization and cleavage rates and follicular fluid endocrinology were assessed in 20 women with mild endometriosis during a spontaneous menstrual cycle. Diagnostic laparoscopy was performed 32 h after the onset of the endogenous luteinizing hormone (LH) surge in the 20 women with laparoscopically confirmed mild endometriosis and in a control group of ten women with tubal infertility. There was no significant difference in oocyte maturity or fertilization and cleavage rates between the women with mild endometriosis and those in the control group. The endocrine milieu of the pre-ovulatory oocyte at the time of aspiration was similar in the two groups.

Mild endometriosis is associated with reduced fecundity (Thomas & Cooke 1987). Reports of fertilization rates in hyperstimulated cycles among women with mild endometriosis are controversial (Wardle *et al.* 1985; Matson & Yovich 1986). There are as yet no data available on fertilisation and cleavage rates in spontaneous cycles in women with mild endometriosis.

Follicular fluid steroids, oestradiol, progesterone and androstenedione, are the main sex hormones surrounding the developing oocyte and have been reported to be important indicators of oocyte maturation and subsequent fertilization in stimulated cycles (Templeton *et al.* 1986). No data are available on the endocrine milieu of the developing pre-ovulatory oocyte in spontaneous cycles in women with mild endometriosis.

In this prospective study fertilization and cleavage rates in women with mild endometriosis were studied and compared with those in the control group of women with tubal infertility during a spontaneous cycle. Sex steroid concentrations (oestradiol, progesterone and androstenedione) in the follicular fluids of the two groups have been compared.

Subjects and methods

Women were selected for this study from a group of 292 women who had had a laparoscopy as part of their investigation for primary infertility (Mahmood & Templeton 1989). This study was approved by the Joint Ethical Committee of Grampian Health Board and University of Aberdeen.

Study group

The study group included 20 women with primary infertility who had mild endometriosis diagnosed at laparoscopy. The median revised AFS score (The American Fertility Society 1985) was 7 (range 2–10). Their ages ranged from 22 to 34 years (median 29 years) and their

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duration of infertility ranged from 3·5 to 7·5 years (median 5·5 years). All had ovulatory midluteal phase serum progesterone concentrations of ⩾30 nmol/l and they all had normal prolactin levels (<600 IU/l) for at least two cycles before entering the study. The partners of 18 women had normal semen analyses (WHO classification, Belsey *et al.* 1980) and the other two partners had azoospermia and the women were attending for artifical insemination by donor.

Control group

Ten women with primary infertility due to pelvic adhesions causing bilateral tubal occlusion were recruited as controls. They were between 24 and 35 years of age (median 31 years) and their duration of infertility was 3–7 years (median 5 years). They all had ovulatory midluteal phase serum progesterone and normal serum prolactin. The partners had normal semen analyses (Belsey *et al.* 1980).

Study design

The women were scanned daily (Diasonic DRF 200 with 7·5 MHz vaginal probe, Diasonic Sonotron, Bedford) from day 5 until the dominant folicle measured >16 mm, then blood samples were taken every 6 h for luteinizing hormone (LH) measurement. The first LH value that exceeded 180% of the mean value of the previous four samples was taken to indicate that the surge had started (Messinis *et al.* 1985) and the time of the immediately preceding sample was considered the time of onset of the surge. A diagnostic laparoscopy was performed between 30 and 34 h (mean 32 h) after the onset of the LH surge.

Oocyte recovery

Each of the 20 women with mild endometriosis had one laparascopy and oocyte recovery; the 10 women in the control group had 12 laparoscopies. A triple puncture technique and a 15 Trendelenburg position was used in each case to undertake follicular aspiration and oocyte recovery. The method for oocyte recovery, fertilization and culture have been reported elsewhere (Papadopoulos *et al.* 1989).

In-vitro fertilization

Semen was collected by masturbation (except in two cases where the cryopreserved semen of a fertile donor was used) into a sterile container, within 4 h of oocyte recovery. A double swim up technique (Wong *et al.* 1986) was used for semen preparation. The oocytes were examined microscopically 16–20 h after insemination, and again 24 h later for evidence of successful fertilization (two or more pronuclei seen) Transcervical embryo transfer was performed if the preembryo was at, or beyond, the four cell stage.

Follicular fluid

The total volume of aspirated follicular fluid was measured. Only the portion of the sample which was not contaminated by blood or culture medium was centrifuged at 2000 rpm for 10 min and aliquots were stored at −40°C for measurement of oestradiol, progesterone and androstenedione.

Hormone assays

Oestradiol concentration in follicular fluid was measured by radioimmunoassay (RIA) (Diagnostic Products Corporation, Los Angeles, USA). The sensitivity of the assay was 80 pmol/l with inter- and intra-assay coefficients of variation between 5% and 9%, and 5% and 8%, respectively.

Androstenedione concentration in follicular fluid was measured by RIA (Coat-a-count, Diagnostic Products Corporation, Los Angeles, USA). The sensitivity of the assay was 0·02 ng/ml and inter- and intra-assay coefficients of variation were between 7% and 10%, and 4% and 7%, respectively.

Progesterone concentration in follicular fluid was measured by RIA (Amerlex-M Progesterone RIA kit, Amersham International, Amersham, UK). The sensitivity of the assay was 1·3 nmol/l with inter- and intra-assay coefficients of variation between 6% and 7%, and 10% and 11%, respectively

Statistical analysis

The data on oestradiol, progesterone and androstendione in the follicular fluid were analysed using Student's unpaired *t*-test. Data on fertilization rate were compared using Fisher's exact test A *P* value of <0·05 was considered significant.

Results

Twenty women with mild endometriosis had a laparoscopy after the onset of the LH surge (Table 1), one had two follicles in the same ovary (one pre-ovulatory follicle with a maximum diameter of 22 mm and a smaller follicle measuring 16 mm maximum diameter). One woman had evidence of spontaneous ovulation at laparoscopy and a mature, grade III oocyte was retrieved from the fluid aspirated from the pouch of Douglas. This oocyte was successfully fertilized. The woman with two follicles yielded two oocytes (one Grade III and one Grade II). No oocyte was retrieved in two women although clusters of granulosa cells were seen in the aspirates of follicular fluid. Thus, a total of 19 oocytes were obtained in this group.

The 10 women with tubal infertility (control group), had 12 laparoscopies (two women had two laparoscopies) and eight oocytes were aspirated. A greater proportion of the oocytes retrieved in the control group had evidence of two pronuclei at 24 h (63%; 95% CI 29–96%) compared with the endometriosis group (53%, 95% CI 30–75%) but the difference was not statistically significant. Once an oocyte was normally fertilized, it cleaved to the 4-cell stage and no pre-embryo was at less than the 4-cell stage when transferred *in utero*. Two oocytes (10%) in the endometriosis group had three pronuclei, compared with none in the control group ($P = 0{\cdot}256$), and they were not transferred *in utero*. There were no clinical pregnancies in either group.

Table 1. Oocyte recovery and fertilization in the two groups

	Study group (endometriosis)	Control group (tubal infertility)
Number of laparoscopies	20	12
Number of women with one follicle	19	12
Number of women with two follicles	1	0
Total number of follicles	21	12
Spontaneous ovulation	1*	0
No oocyte retrieved	2	4
Number of oocytes		
Identified	19 (90%)	8 (66%)
Grade III maturity	18	8
Grade II maturity	1	0
Fertilization data at 24 h†		
Oocytes with two pronuclei	10/19 (53%)	5/8 (63%)
Oocytes with three pronuclei	2/19 (10%)	0/8 (0%)
Unfertilized oocytes	7/19 (37%)	3/8 (37%)

* A mature oocyte retrieved from the aspirate of the pouch of Douglas

† There are no significant differences at 5% level using Fisher's exact test between the two groups.

The mean follicular fluid volume was significantly greater in the endometriosis group than in the control group (Table 2). However, concentrations of oestradiol, progesterone and androstenedione were not significantly different between the two groups (unpaired *t*-test).

Discussion

The overall fertilization and cleavage rates among women undergoing IVF in hyperstimulated cycles vary between 67% and 78% in women with tubal infertility (Dor *et al.* 1986) or in those with endometriosis (Brinsmead *et al.* 1989); in a group of previously fertile women undergoing laparoscopic sterilization and taking part in an oocyte donation study the rate was 77 to 80% (Templeton *et al.* 1986). There are no reported data on the fertilization and cleavage rate in spontaneous cycles in women with mild endometriosis. Although only a relatively small number of women were studied, we found that egg maturity, fertilization and cleavage rates in women with mild endometriosis were similar to those in the control group. Even if the observed difference of 10% in fertilization rates in our

Table 2. Follicular volume and sex steroid levels in the two groups

Variables	Study group (endometriosis) Mean (SEM)	Control group (tubal infertility) Mean (SEM)
Follicular volume (ml)	5·12 (0·25)	4·18 (0·26)*
Oestradiol (nmol/l)	2852 (351)	2919 (458)
Progesterone (nmol/l)	31873 (2314)	29272 (2289)
Androstenedione (nmol/l)	170 (23)	240 (71)

* $P = 0{\cdot}024$, unpaired *t*-test.

study and control groups was real, a large number of women (380 in each group) would be required to confirm this point (α 0.05; β 0.20; power 0.80: Pocock 1985).

The occurrence of oocytes with three pronuclei has been reported ranging from 5 to 12% in hyperstimulated cycles in IVF programmes (Wentz *et al.* 1983; Plochot *et al.* 1987). Possible reasons include inadequate pre-incubation before insemination, insemination with high sperm concentrations and ageing of the oocytes, with delayed fertilization in-vivo or in-vitro. However, in our study all the women had follicular aspiration 32 h after the onset of an endogenous LH surge and only mature oocytes were pre-incubated for 4–6 h before insemination. Two oocytes in the endometriosis group had three pronuclei as opposed to none in the control group but the number of oocytes was small and definite conclusions cannot be drawn regarding the occurrence of abnormality in women with mild endometriosis.

The endocrine milieu surrounding a pre-ovulatory oocyte may affect its potential for fertilization and cleavage. Low androstenedione levels in the follicular fluid may reflect oocyte maturity (Brailly *et al.* 1981; Templeton *et al.* 1986). High oestradiol levels are associated with an increased cleavage rate in-vitro and low levels were noted with unfertilized oocytes (Lee *et al.* 1987; Subramanian *et al.* 1988) Basuray *et al.* (1988) found high progesterone levels in the follicles of women who conceived compared with a group who did not. Our study found no significant differences in the levels of follicular fluid steroids between women with mild endometriosis and those with tubal infertility.

We conclude that whatever defects militate against fertility in women with mild endometriosis they do not appear to involve folliculogenesis and oocyte maturation. These findings are important in directing attention to other areas in an attempt to explain the association between endometriosis and infertility.

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Immunoreactive endometritis

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Summary. A benign polyclonal lymphoid proliferation of the endometrium which bears morphological resemblance to the malignant lymphoma is found among women with bleeding disturbances. Seven previous cases have so far been reported in the literature. A retrospective examination of 11 648 endometrial specimens revealed 287 examples of chronic endometritis (2·5%) of which 29 displayed lymphoid proliferation. We found no evidence of malignant haematologic disorder after a median observation of 68 months and no positive association with prior or present infectious disease. Histological follow-up of ten patients showed that changes could persist for up to 12 months. We name this benign condition 'immunoreactive endometritis'.

Occasionally, women with menstrual disturbances are found to have an endometrium infiltrated by large lymphocytes, immature plasma cells and immunoblasts, histologically resembling a non-Hodgkin's lymphoma (Young *et al.* 1985).

So far descriptions of only seven such endometrial lesions have been published: five reported by Young *et al.* (1985), a case report by Larsen *et al.* (1981) and another case report by Thomas (1986). An infectious aetiology is suggested by Young *et al.* (1985) (Epstein-Barr-virus) and Thomas (1986) (*Chlamydia trachomatis*). We review the histopathology and clinical course of 29 patients with such lymphoma-like lesions of the endometrium and argue in favour of the use of the term immunoreactive endometritis for this histological entity.

Patients and methods

Curettage or hysterectomy was performed on 11 648 patients from Ringkjoebing county (catchment area: 275 000) between 1976 and 1985.

All specimens were stored in 10% buffered formalin, paraffin-embedded and cut into 4 μm thick sections. Haematoxylin-eosin and May-Grunewald-Giemsa stains were used routinely. Fifteen specimens were also investigated by immunohistochemical staining for immunoglobulin kappa and lambda light chains with polyclonal rabbit antibodies (Dako, Copenhagen) and the direct immunoperoxidase technique (Bourne 1983).

We examined from one to nine sections (median 2) from each patient. All microscopic fields were examined (×400 magnification) and all sections analysed by the three authors.

Chronic endometritis was defined as the presence of diffusely infiltrating or focally localized plasma cells in the endometrial stroma (Vasudeva 1972).

The criteria for a lymphoma-like lesion (immunoreactive endometritis) was a stromal infiltration with activated lymphoid cells, immature plasma cells and immunoblasts. Based on the nature of the infiltration, the lesions were further divided into two subgroups: a diffuse form in which the infiltration was uniform throughout the specimen, and a focal form in which the lymphoid cells, plasma cells and

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immunoblasts were found locally in well-defined cellular congregations in the endometrium.

Medical histories were obtained from the clinical records, the central county patient register and from referral letters of general practitioners.

Results

Of the 11 648 specimens examined 287 (2·5%) met the criteria of chronic endometritis.

The diagnosis was established from curettings in 280 patients and from hysterectomy specimens in the other seven. In specimens from 29 patients (10%), lymphoma-like proliferative lesions were found; the diffuse type in 15 and the focal type in the other 14. All diffuse lesions exhibited changes in 75–100% of the microscopic fields and all focal lesions showed changes in >50% of the fields.

In two of the specimens with diffuse changes the immunoproliferative process had crowded out the underlying stroma almost completely and plasma cells were few and scattered. Reed-Sternberg-like cells or intranuclear virus particles were not observed. Endometrial glands often showed proliferation with intraepithelial granulocytes and mononuclear cells (Fig. 1).

Immunohistochemical staining for immunoglobulin kappa and lambda light chains was positive in 15 specimens, confirming the polyclonal, benign nature of the lesion.

Key points of the medical histories are as follows.

The median age of the 29 women was 29 years (range 21–43) and the median number of pregnancies was 3 (range 0–4). Previous pelvic inflammatory disease was reported (but not verified by culture growth) in 5 (17%), the other 24 had no history of PID. Use of contraception within 12 months before symptom onset was: none in 13 (45%); hormonal in 8 (28%); intrauterine contraception in 2 (7%); others in 1 (3%) and unknown in 5 (17%).

All 29 patients presented with metrorrhagia with a median duration of symptoms of 6 months (range: 2–14). None had had any previous or suspected autoimmune or haematological disorder.

Four of the six patients who had had a fractional curettage sometime before the actual curettage or hysterectomy were observed during the intervening period (median 18·5 months), but none of them showed signs of severe infection or mononucleosis.

Twenty-eight of the patients were normal on physical examination and had body temperatures and erythrocyte sedimentation rates (ESR) within the normal ranges. No cultures or serologic titres were obtained from these 28 patients. One patient had evidence of active inflammation on admission (tender uterus, slight fever, ESR=40, *Chlamydia trachomatis* titre increasing from 60 to 120). Blood samples from this patient provided evidence of a previous, but not of any current, infection with Epstein-Barr virus (EBV) and cytomegalovirus (EBV: IgG positive, IgM negative; CMC: IgG positive and IgM negative).

Clinical follow-up (median 68 months, range 32–132 months) was available for all the patients. None had any actual signs nor was there any suspicion of a malignant haematological disorder.

Histological follow-up was available for ten patients (Table 1).

Some 90% of the population of Scandinavia over 20 years of age are EBV IgG positive (Ström 1987) and a retrospective examination of EBV titres in the 29 patients reported here would thus hardly be expected to shed additional light on the nature of relevant aetiologic factor(s).

Discussion

Normal endometrial stroma contains lymphoid tissue consisting primarily of T-lymphocytes, macrophages and a few scattered B-lymphocytes (Kamat & Isaacson 1987), but rarely immunoglobulin-secreting plasma cells (Kelly & Foss 1979).

Payan *et al.* (1964) claim the presence of lymphoid follicles in the normal endometrium; an observation which others have not been able to confirm (Marshall & Jones 1988). Morris *et al.* (1981) advocate the use of the description ‘mucosal associated lymphoid tissue’ (MALT). The lymphoma-like lesion possibly represents an antigen-stimulated proliferation of this endometrial-associated lymphoid tissue. Epstein-Barr virus (Young *et al.* 1985) and *C. trachomatis* (Thomas 1986) have been suggested as possible triggering antigens.

The endometrial stroma, with its dense infiltration of large lymphoid cells, mature lymphocytes, immunoblasts, immature and mature

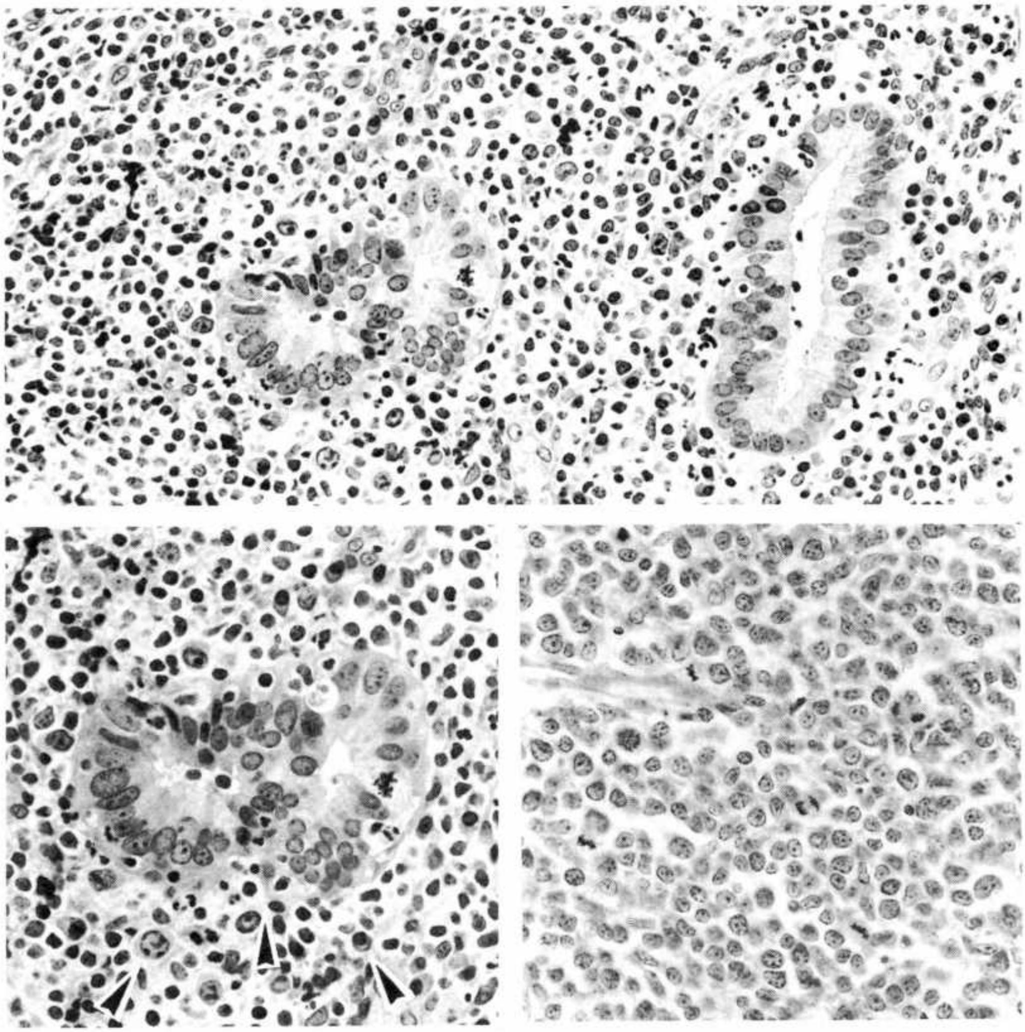

Fig. 1. Top and lower left: Endometrium from a 29-year-old woman with diffuse immunoreactive endometritis (IREM). There is a polymorphic infiltrate with numerous immunoblasts (left arrow), immature plasma cells and mature plasma cells (right arrow). Glands show destruction of the basement membrane (middle arrow), intraepithelial invasion by lymphoid cells, reactive epithelial changes and mitoses. Original magnification ×250 (top) and ×400 (lower left).
Lower right: Endometrium from a 26-year-old woman with diffuse immunoreactive endometritis (IREM), showing polymorphic lymphoid infiltrate and numerous mitoses. Original magnification ×630.

plasma cells, bears a strong resemblance to that of lymph nodes in infectious mononucleosis in all of our 29 specimens. However, we have not been able to identify data supporting any positive association with infectious disease. Indeed, we have the following negative data on the lack of association with infection: (i) in 24 of the 29 women there was no evidence of previous pelvic inflammatory disease and in the five women with a positive history of PID the diagnosis was based solely on clinical observation with no culture or serologic verification; (ii) none of the four patients who had a fractional curettage before the actual curettage showed any clinical signs of severe infection or autoimmunological disease in the intervening period; (iii) at the time of diagnosis only one of the 29 patients presented with signs of acute PID (although none of the remaining 28 patients were tested to rule out subclinical infection).

Table 1. Histological follow-up in 10 patients

Patient	Initial diagnosis	Follow-up appearance
1	C, focal IREM	1st: C, 2 months, unspecific chronic endometritis
2	C, focal IREM	1st: H, 3 months, focal IREM
3	C, focal IREM	1st: H, 2 months, unspecific chronic endometritis
4	C, diffuse IREM	1st: C, 39 months, no endometritis
5	C, diffuse IREM	1st: C, 18 months, unspecific chronic endometritis 2nd: H, 21 months, no endometritis
6	C, diffuse IREM	1st: H, 18 months, diffuse IREM
7	C, diffuse IREM	1st: H, 6 months, diffuse IREM
8	C, diffuse IREM	1st: H, 3 months, no endometritis
9	C, diffuse IREM	1st: C, 7 months, diffuse endometritis
10	C, diffuse IREM	1st· C, 4 months, diffuse IREM 2nd: C, 12 months, focal IREM 3rd: C, 30 months, no endometritis

C=curettage; H=hysterectomy; IREM=immunoreactive endometritis.

Studies of the prevalence of chronic endometritis have come up with widely differing results despite the application of identical criteria. For example, this was 2·8% in the study by Vasudeva (1972) but 8% in that by Greenwood & Moran (1981).

We found a prevalence of non-specific chronic endometritis of 2·5% in our specimens. Of the 287 cases with non-specific endometritis 10% had immunoproliferative changes (5·2% diffuse, 4·9% focal).

We cannot judge whether this occurrence is higher than expected since there have been no systematic studies of the prevalence of these changes in the endometrium. For example, Thomas (1986) reported a case of immunoreaction associated with *C. trachomatis* which was later reclassified as *C. endometritis*, but Young (1985) reported 16 cases (including non-endometrial cases) of which four were classified as malignant lymphoma.

Our observations may be summarized as follows: the lymphoma-like lesion involves the cellular components of the immunological system and the nuclei lack the features of malignancy: they do not show light chain restriction but are polyclonal and not monoclonal as in neoplastic proliferations. Clinically, the condition is transient with none of the patients developing a lymphoma. Hence we find the term 'immunoreactive endometritis' appropriate for this lesion.

The differential diagnosis of immunoreactive endometritis from malignant lymphoma rests essentially on the characteristics outlined by Young *et al.* (1985). Firstly, lymphocytes are polyclonal in immunoreactive endometritis, but consist of one or two-cell clones in malignant lymphoma. Secondly, the benign state of the endometrium is characterized by the dominantly superficial location of the lymphocytic infiltration which allows the lesion to reach the ulcerated outer stratum. In contrast, the lymphoma infiltrates the deeper mucosal and myometrial strata. Thirdly, the fibrosis, which often accompanies malignant lymphoma, is not seen in immunoreactive endometritis. Finally, immunoreactive endometritis is secondary to chronic endometritis and the concurrent presence of plasma cells confirms the benign nature of this lesion.

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Acute recurrent polyhydramnios—management with indomethacin

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Case Report

A 28-year-old woman had had two previous pregnancies elsewhere. The first in 1981 ended in spontaneous labour at 29 weeks in association with polyhydramnios of rapid onset and a normal male child weighing 1250 g was born vaginally. Amniocentesis in labour allowed the removal of 2·5 litres of amniotic fluid. In the second pregnancy in 1982 polyhydramnios developed rapidly at 28 weeks. A glucose tolerance test and a fetal ultrasound examination were normal before labour at 29 weeks. Amniocentesis was performed in early labour and 1 litre of amniotic fluid was removed. Tocolysis and corticosteroid therapy were also used. A male child weighing 1420 g was born using forceps. This second child has a bilateral sensory hearing impairment and a left sided hemiparesis.

In the index pregnancy, she booked for antenatal care at 9 weeks gestation. She disclosed that she had two epileptic first cousins. There was no abnormality on general examination. The uterus was bicornuate and the cervix long and closed. Rapidly developing polyhydramnios was recognized at 25 weeks but there were no uterine contractions or pressure effects. She was admitted for detailed assessment.

Investigation showed rubella immunity, an O Rh negative blood group, no irregular blood antibodies and negative screening for syphilis. Full blood counts, serum alphafetoprotein (AFP) assay, a 75 g glucose tolerance test, liver function tests and urea and electrolytes assays proved satisfactory. Viral screening, including TORCH, was negative. Diagnostic amniocentesis (20 ml) indicated a 46XX fetal chromosome complement and a normal AFP level with single-band gel cholinesterase. Tissue typing showed common HLA antigens B7, BW6, DR2 and DR3 between the parents. Ultrasound revealed no fetal abnormality or placental chorioangioma.

At 26 weeks the patient complained of abdominal discomfort and further abdominal distension, associated with uterine contractions and slight vaginal bleeding. The uterus was term-size with a fluid thrill and fetal parts were impalpable. The cervix was long, closed and normal in appearance. She was treated with oral indomethacin, 175 mg/day (2 mg/kg body weight).

Therapy was monitored in the mother by white cell and platelet counts and urea and electrolyte estimations twice weekly and by ophthalmic examination weekly. The urinary output was measured daily. No untoward changes were observed. The fetus was monitored by twice weekly biophysical profiles and Doppler blood flow waveforms in the umbilical vessels. At each of these examinations the patency of the fetal ductus arteriosus and filling and emptying of the fetal bladder were studied. All these observations remained satisfactory. Daily fetal movement counts and twice weekly cardiotocography proved normal, although the latter was sometimes technically difficult during periods of marked polyhydramnios.

Contractions ceased quickly after introducing indomethacin, the uterus became smaller and softer and fetal parts became readily palpable. There were no maternal gastrointestinal symptoms. Response to treatment was judged by maternal pressure symptoms, weekly measurement of the symphysis fundal height (Fig.1), and

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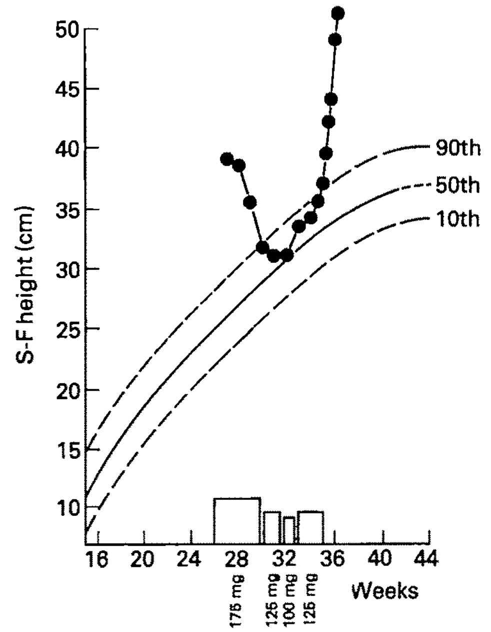

Fig. 1. Symphysis-fundal (S-F) height measurements during and after treatment with indomethacin (between 100 and 175 mg/day) superimposed on the normal curve based on Cardiff data from Calvert *et al* (1982).

twice weekly ultrasound measurement of the depth of the largest pocket of amniotic fluid (Fig.2).

The dose of indomethacin was titrated against amniotic fluid volume in an attempt to maintain the depth of the largest pocket of fluid between 2 and 8 cm. Epigastric pain and heartburn developed at 35 weeks and indomethacin was discontinued. Five days later amniotic fluid volume had increased greatly, causing abdominal discomfort and orthopnoea. Pressure symptoms worsened and amniocentesis was performed under ultrasound control. Two litres of fluid were drained over 4 h.

At the end of the procedure, lower abdominal pain and tenderness were evident. Ultrasound failed to demonstrate placental abruption but revealed fluid anterior to the lower part of the uterus. Later, a collection of fluid, assumed to be amniotic, was identified clinically in the anterior abdominal wall. Uterine contractions developed over the next 3 h and a good quality suboptimal cardiotocograph was obtained. The lecithin-sphingomyelin ratio was 4·3 (lung maturity >5).

Next morning, at 36 weeks and 2 days, labour began spontaneously and cardiotocography showed a reactive pattern. The fluid in the abdominal wall had disappeared. After a first stage of 75 min and a second stage of 18 min, a live female child was born weighing 2575 g and having an Apgar score of 9 at 1 and 5 min. There was no problem with post partum haemorrhage. The placenta weighed 710 g and the umbilical cord contained three blood vessels. There was no chorioangioma and histopathology of the placenta was normal.

The baby was Rh negative and was observed in the special care baby unit. A nasogastric tube was passed easily at birth. A full blood count, including platelets, serum urea, serum creatinine, serum electrolytes, and serum bilirubin together with a coagulation screen were satisfactory. Urine output and an ultrasound scan of the kidneys were normal. The infant is developing normally and is now 6 months old.

Discussion

Acute polyhydramnios is uncommon, is said to occur in 1 in 12 000 pregnancies (Pitkin 1976) and accounts for 1·7% of all cases of polyhydramnios (Queenan & Gadow 1970). It is characterized by virtually certain perinatal death

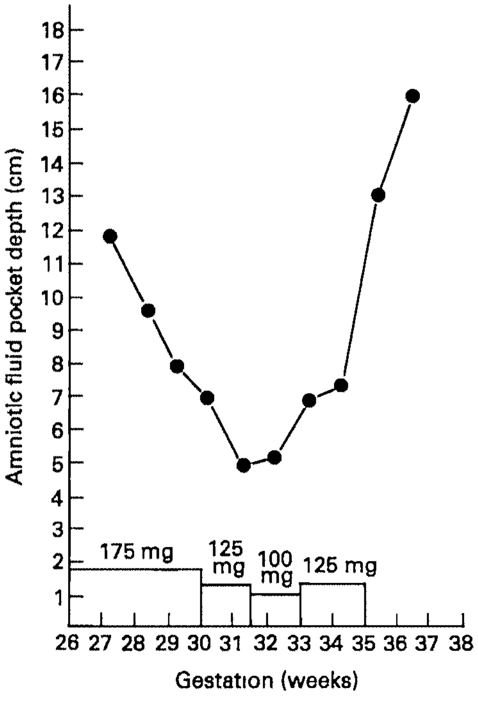

Fig. 2. Amniotic fluid pocket depth in relation to indomethacin use (oral indomethacin was given at doses of 100 mg to 175 mg per day).

(Queenan & Gadow 1970; Pitkin. 1976) and severe maternal effects (Queenan & Gadow 1970). It is mostly without a defined cause but fetal polyuria may be of aetiological importance (Sieck & Ohlsson 1984; Schneider *et al.* 1985; Boylan & Parisi 1986).

Acute polyhydramnios is associated with subjective and imprecise clinical features (Queenan & Gadow 1970). However, ultrasound has helped to define hydramnios more objectively in terms of pocket depth (Chamberlain *et al.* 1984). The acute variety is usually treated urgently and often unsuccessfully by amniocentesis to relieve maternal symptoms and to prolong pregnancy, although the latter consideration seems to have been largely secondary. Acute recurrent polyhydramnios is extremely rare but, in a particular woman, a history of this condition may afford an opportunity for management in a subsequent pregnancy.

Four reports of acute recurrent polyhydramnios have been identified in the literature, each idiopathic (Queenan 1970; Pitkin 1976; Weissman & Zimmer 1987 and Shimizu *et al.* 1988) and our patient, also idiopathic, provides another example. Shimizu *et al.* (1988) postulated an immunological cause for acute recurrent polyhydramnios based on parental compatibility of human leucocyte antigens. Four common parental human leucocyte antigens were noted in this case, and in addition, the increased placental/fetal ratio raises the possibility that excessive secretion of fluid across the fetal surface of the placenta may have contributed to the polyhydramnios.

Amniocentesis is the principal recommended means of management of acute recurrent polyhydramnios, having been performed up to 27 times and removing as much as 20 litres of amniotic fluid in a single pregnancy. This form of management is associated with significant perinatal mortality and preterm delivery (Queenan 1970; Pitkin 1976; Weissman & Zimmer 1987; Shimizu *et al.* 1988).

Amniocentesis falls short of the ideal, since it may be associated with serious complications. Initiation of labour, placental abruption, amnioitis and hypoproteinaemia are potential hazards (Queenan 1970), as is trauma to the fetus, cord and placenta. Weissman & Zimmer (1987) expressed concern about possible harmful effects of repeated amniocentesis. An alternative is to use indomethacin, a non steroidal anti-inflammatory drug and a prostaglandin synthesis inhibitor to reduce amniotic fluid volume and to prevent or treat associated preterm labour.

Non-steroidal anti-inflammatory drugs, including indomethacin, have been used outside Britain to treat polyhydramnios and preterm labour (Dudley & Hardie 1985; Niebyl *et al.* 1986; Cabrol *et al.* 1987; Kirshon *et al.* 1988; Hickok *et al.* 1989 & Lange *et al.* 1989). These preparations reversibly reduce amniotic fluid volume (De Wit *et al.* 1988; Goldenberg *et al.* 1989; Hickok *et al.* 1989 & Hendricks *et al.* 1990) and Goldenberg *et al.* (1989) suggested that this effect may be dose related. There is some evidence from our patient to substantiate the latter view.

The effect of these anti-inflammatory drugs on amniotic fluid volume may be due to reduction in fetal urine output as Kirshon *et al.* (1988) showed reversible diminution of fetal urine production during treatment of preterm labour with indomethacin. This observation probably follows changes in glomerular filtration rate, and Cifuentes *et al.* (1976) demonstrated a 27% fall in newborn babies given indomethacin to treat patent ductus arteriosus. However, reduced fetal urine production may also be mediated by indomethacin interfering with the peripheral blocking effect of prostaglandin on antidiuretic hormone (Cifuentes *et al.* 1979) or by influencing prostaglandin control of its central release (Gagnon *et al.* 1973). Yet other actions of these drugs may influence amniotic fluid volume, including increased absorption in the fetal respiratory tract and altered fluid transfer across the amniotic membranes (Cabrol *et al.* 1987).

Fears of the fetal and neonatal effects of non-steroidal anti-inflammatory therapy in pregnancy are probably the main reasons for its unpopularity in Britain. It has been suggested that these effects contra-indicate the use of the preparations (Lancet 1980). Intrauterine closure of the ductus arteriosus has occurred in association with the use of prostaglandin synthesis inhibitors (Niebyl 1981). Kirshon *et al.* (1988) discontinued indomethacin in three of eight patients treated for preterm labour because of transient fetal ductus arteriosus constriction. Primary pulmonary hypertension occurred in two infants after indomethacin therapy in preterm labour (Manchester *et al.* 1976). Goudie & Dossetor (1979) reported a case of persistent fetal circulation in association with indomethacin therapy.

In the newborn, non-steroidal anti-inflammatory drugs given to induce constriction of a patient ductus arteriosus caused oliguria and depression of renal function (Cifuentes *et al.* 1979). These changes reversed after stopping treatment and there were not any long term sequelae. Indomethacin inactivates cyclooxygenase and interferes with platelet function. However, this effect is quickly reversed as drug levels fall (Niebyl 1981). The latter author also indicated that indomethacin may displace bilirubin from albumin, increasing the risk of bilirubin toxicity in the newborn.

Kirshon & Cotton (1988) observed normal ductus arteriosus function echocardiographically during 9 weeks of therapy with indomethacin for polyhydramnios, and this was also true for our patient. Cabrol *et al.* (1987) and Lange *et al.* (1989) saw no adverse fetal effects in 14 patients, including six twin pregnancies, treated with indomethacin for polyhydramnios or preterm labour. In addition, Dudley & Hardie (1985), Niebyl & Witter (1986) and Hendricks *et al.* (1990) did not encounter any adverse fetal effects with the use of these drugs in preterm labour.

Maternal gastrointestinal side effects occur with oral or intravenous use of prostaglandin synthesis inhibitors but can be reduced by rectal administration (Niebyl 1981). Nevertheless, there is a potential for serious maternal complications from therapy that necessitates careful observation and might lead to treatment being discontinued.

The view that non-steroidal anti-inflammatory drugs are contra-indicated in pregnancy appears extreme, since indomethacin is effective therapy for both polyhydramnios and preterm labour. However, it would seem sensible to use the lowest effective dose, intermittently if possible, and to discontinue treatment when delivery is considered safe.

On balance, there appears to be limited danger to the fetus and newborn infant from indomethacin exposure in pregnancy. Its effect on the ductus arteriosus may diminish as pregnancy advances (*Lancet* 1980) and can be monitored. However, it is probably unwise to consider this vessel in isolation and ideally the function of other important arteries should also be observed unless the ductus arteriosus can be shown to serve as an adequate marker for them. Additional fetal and neonatal side effects are usually transient and reversible, and oligohydramnios seems more likely when treating preterm labour than polyhydramnios. Clearly, awareness of maternal problems is important and their occurrence may necessitate cessation of treatment.

Indomethacin should be used in minimal effective dosage until delivery is considered possible and safe. However, recurrence of polyhydramnios is likely after the drug is stopped and this poses the threat of directly related complications unless labour ensues quickly or is induced. Continued use of indomethacin may delay or prevent the onset of labour.

Chronic polyhydramnios is much more common than the acute form. It too may lead to fetal morbidity and mortality. Administration of indomethacin might usefully be considered in more severe cases to reduce these possibilities. It certainly offers a rational alternative to repeated amniocentesis in the management of the acute variety.

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Is large loop excision of the transformation zone (LLETZ) more accurate than colposcopically directed punch biopsy in the diagnosis of cervical intraepithelial neoplasia?

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Summary. In 100 women with suspected cervical intraepithelial neoplasia (CIN) attending the colposcopy clinic the histological diagnoses made from excision biopsies taken by large loop excision of the transformation zone (LLETZ) were compared with those from colposcopically directed punch biopsies taken concurrently. One unsuspected microinvasive tumour was found and the diagnosis made by LLETZ was significantly worse than that made by punch biopsy in 24 cases (24%: 95% CI 15·6 to 32·4%). LLETZ improves the accuracy of diagnosis of CIN.

In order to treat cervical intraepithelial neoplasia (CIN) safely by local ablative methods the severity of the lesion must first be diagnosed accurately. In particular, invasive disease must be excluded. Kirkup *et al* (1980) reported good correlation between colposcopically directed punch biopsies and subsequent definitive diagnosis by cone biopsy or hysterectomy. In 98% the definitive severity of cervical dysplasia was not more than one degree greater than on punch biopsy; all microinvasive tumours were correctly identified. They considered that colposcopically directed biopsies provided adequate assessment. More recent studies have contradicted this contention and suggested that a significant proportion of microinvasive or occult invasive tumours remain unrecognized by colposcopy and punch biopsy and may therefore be inappropriately or inadequately treated by local ablation. In a review of 26 patients with microinvasive tumours, Choo *et al.* (1984) found that only 26% were correctly recognized visually at colposcopy, and four of the 22 patients with a fully visible transformation zone had punch biopsies which failed to detect microinvasion, subsequently diagnosed by cone biopsy or hysterectomy. Further evidence was provided by McIndoe *et al.* (1989) who noted a fall in the rate of diagnosis of microinvasive disease following the introduction of ablative treatment, suggesting that unrecognized tumours were being destroyed. They advised a return to treatment of CIN by excision, recommending laser cone as the treatment of choice. They suggested that this outpatient procedure combined the advantages of more accurate diagnosis with the low morbidity of local ablation. In their study 119 women had punch biopsies taken before treatment by laser cone at a subsequent visit: there were two undiagnosed microinvasive tumours and 16 women had lesions two or three grades worse than predicted by punch biopsy. Since then Prendiville *et al.* (1989) have described the technique of LLETZ (large loop excision of the transformation zone) using equipment much

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Table 1. Diagnoses from loop and punch biopsies in 100 women

	Loop biopsy						
Punch biopsy	No CIN	HPV	CIN 1	CIN 2	CIN 3	Micro-invasion	Total
No CIN	9	8	6	9	3	–	35
HPV	–	3	1	2	1	–	7
CIN 1	–	–	5	6	–	–	11
CIN 2	–	–	1	20	11	–	32
CIN 3	1	–	–	1	12*	1	15
Total	10	11	13	38	27	1	100

*Adenocarcinoma-in-situ identified in one loop biopsy.
CIN, cervical intraepithelial neoplasia.
HPV, human papillomavirus

cheaper to buy and maintain than a laser and they suggested that LLETZ will produce a similar improvement in the accuracy of diagnosis of CIN. Our study was designed to investigate this claim.

Subjects and methods

The study included women referred with abnormal smears to the Royal Hampshire County Hospital, Winchester from November 1989 to August 1990. Women were referred to the colposcopy clinic after a single cervical smear showing moderate or severe dyskaryosis; women with mild dyskaryosis had repeat smears at intervals of 6 months and referral for colposcopy was recommended if the abnormality persisted in two subsequent smears. Most of the colposcopic examinations were performed by two registrars each with one year's previous experience of colposcopy; the remainder were done by consultants. If an epithelial abnormality suggestive of CIN was seen, a directed biopsy was taken from the worst apparent area with Eppendorfer forceps, immediately before LLETZ using the technique described by Prendiville *et al.* (1989). Several punch biopsies were taken if the area of atypicality was large. Most treatments were performed in the colposcopy clinic under local anaesthesia, but if a very large area required treatment it was done as an inpatient procedure under general anaesthesia. Prophylactic oral doxycycline 100 mg and triple sulphonamide cream (Sultrin) one applicator at night were prescribed for one week after treatment. Although LLETZ can be used as an alternative to knife cone biopsy, patients were excluded from the study if they were unsuitable for local ablative treatment because the transformation zone was not fully visible, invasive disease was suspected, or they could not attend for follow-up.

All specimens were examined by the same pathologist (A.C.V.). The women gave informed consent and the study was approved by the local ethics committee.

Results

Overall 100 women were included in the study. Table 1 shows the correlation between loop biopsy and punch biopsy results. In only three cases was the diagnosis worse on punch biopsy, presumably because the worst focus of abnormality had been removed. One woman was found to have an unsuspected focus of microinvasive carcinoma after a smear showing moderate dyskaryosis and a punch biopsy showing CIN 3. The maximum depth of invasion was <1 mm and the carcinoma appeared completely excised, but because the neoplastic area extended to the margin of excision she had a total abdominal hysterectomy subsequently. Histology revealed residual CIN 3 and another minute focus of microinvasion of <1 mm depth with no involvement of lymphatic or vascular spaces. At the time of the hysterectomy she was found incidentally to have a carcinoid tumour of the appendix, which was also removed. Another woman was found to have adenocarcinoma-in-situ on the loop biopsy after CIN 3 was found by punch biopsy. Excision appeared complete and no further treatment was given.

Table 2 shows the completeness of excision of CIN in loop biopsy specimens. Of the 80 women with CIN, the lesion was completely excised in

Table 2. Histological assessment of completeness of excision of CIN

Excision complete	53
Excision incomplete	11
Excision uncertain	16
No CIN	20
Total	100

53 (66%), incompletely excised in 11 (14%), with excision uncertain in 16 (20%).

No woman suffered excessive bleeding at the time of treatment, and none of the women treated as outpatients required admission. One woman was admitted 4 days after treatment with secondary haemorrhage, and required further diathermy to control the bleeding.

Kirkup *et al.* (1980) considered a difference of two grades of CIN, or more, to be significant. We considered it significant if punch biopsies were negative and CIN was found in the loop specimen, and when punch biopsies failed to identify microinvasion or adenocarcinoma-in-situ. In 22 women, loop biopsies showed CIN but punch biopsies showed only squamous metaplasia or human papilloma virus infection: 4 had CIN 3, 11 had CIN 2, and 7 had CIN 1 (in 15 of these women the diagnosis obtained by loop biopsy was at least two grades worse). Including the woman with unrecognized microinvasion and adenocarcinoma-in-situ, there were, therefore, 24 cases (24%: 95% CI 15·6–32·4%) in which the loop biopsy resulted in significant alteration of the diagnosis.

The colposcopic findings in the 20 women who had no CIN on either loop or punch biopsy were reviewed. Eleven had changes due to human papilloma virus infection which were misinterpreted colposcopically as CIN. Three were new referrals with moderate dyskaryosis in cervical smears and atypia suggestive of CIN found at colposcopy (one had only a shallow loop biopsy taken initially but CIN 2 was found at her first follow-up visit suggesting that the original loop specimen was inadequate; in the other two there was no histological evidence of CIN despite the abnormal smear report). One woman had four mildly dyskaryotic smears over a period of 2 years before treatment. The remaining five had all undergone previous treatment by needle and ball diathermy or cold coagulation for CIN 2 (three women), or CIN 3 (two women). Of these, three had recurrent abnormal cervical cytology and apparent colposcopic atypia; one had changes strongly suggestive of CIN at first follow-up colposcopy after treatment by needle and ball diathermy; the other woman had been abroad, without follow-up, for 2 years since treatment by needle and ball diathermy for CIN 3 and had colposcopic atypia suggestive of recurrent dysplasia.

Discussion

Prendiville *et al.* (1989) showed that LLETZ is an acceptable outpatient procedure with advantages similar to those of local ablation over knife cone biopsy. They suggested that providing the entire tansformation zone for histology would improve the accuracy of diagnosis of CIN. Our study supports their contention. Another advantage of LLETZ is that complete excision may be histologically confirmed. In the 16 women in whom complete excision was uncertain the most common reason for uncertainty was that the transformation zone had been too large to remove in a single piece and the pathologist was unable to orientate the fragments. This is a disadvantage compared with laser excision whereby even large areas can be excised in a single cone of tissue. Pinning out the fragments, correctly orientated, at the time of LLETZ might have reduced the proportion with uncertain completeness of excision.

The histological grading of CIN is dependent on many factors, and it is well recognized that different pathologists may apply different grades to the same specimen. To ensure consistent reporting all our specimens were examined by the same pathologist (A.C.V.).

This study is open to the criticism that the colposcopists were relatively inexperienced and that the punch biopsies may not therefore have been accurately directed. However, our results are similar to those of McIndoe *et al.* (1989) who reported that 14% of their patients had a negative punch biopsy with CIN in the laser cone; 13% had laser cone results two or more grades worse than on punch biopsy. A higher proportion of their patients had lesser grades of CIN in the cone than on punch biopsy; this may be the result of the 2 weeks' delay between punch biopsy and laser cone treatment and the destruction of surrounding areas of CIN by cautery to stop bleeding after the biopsy. By taking our punch biopsies at the same time as the loop biopsy we provided directly comparable results. Previous studies, such as that of Kirkup *et al.*

(1980), showing close correlation between punch and cone biopsies have emanated from expert centres which may not be representative of the general level of expertise. If the discrepancy between loop and punch biopsies which we found is partly due to the inexperience of the colposcopists then the argument for using excision techniques in hospitals where there is a turnover of staff, with varying levels of skill, is strengthened.

Luesley *et al.* (1990) reported a large study of 616 women treated by LLETZ and were accused of overtreating a high proportion of women in whom no CIN was found on histology (Ismail 1990; Hillier 1990). In reply, Luesley (1990) ascribed the large numbers found to have only koilocytic atypia partly to the increased histological accuracy of loop specimens: koilocytosis may be misinterpreted as CIN in punch biopsies. It is debatable whether koilocytosis alone requires treatment but many women who are very concerned about persistently abnormal smears might not consider LLETZ overtreatment if their subsequent smears were normal. It is interesting to note that of the nine women in our study without koilocytosis or CIN over half had undergone previous treatment by local ablation: the resultant scarring may be confusing both cytologically and colposcopically. Any screening technique will report a proportion of false positive results and in three of the other four women without koilocytosis or CIN the cytology was misleadingly pessimistic.

Our study confirms that LLETZ improves the accuracy of diagnosis of CIN We have found it easy to use and acceptable as an outpatient procedure. Luesley *et al.* (1990) showed a low rate of early complications: 4·3% had secondary haemorrhage and 1·3% were found to have severe cervical stenosis at first follow-up. McIndoe *et al.* (1989) have advocated a return to treatment by excision but before LLETZ can be recommended as the treatment of choice a much larger study is necesary to compare it directly with ablative treatment with regard to the efficacy and complication rate. As might be expected Luesley *et al.* (1990) found cervical stenosis was more likely with deeper excision. Their follow-up period was too short to detect late complications such as cervical incompetence but a similar relation is possible. It is our impression that loop diathermy causes deeper damage to the cervix than the Semm cold coagulator which we used previously and this may result in a higher incidence of late complications with LLETZ. The microinvasive tumours reported by McIndoe *et al.* (1989) and in our study were small, none had invaded deeper than 1·4 mm and would probably have been adequately treated by ablation. Therefore, although histological grading of CIN may be improved by a return to treatment by excision it has yet to be shown that this will result in improved outcome. A large proportion of women who require treatment for CIN are young and have not yet completed their families. If excision results in a significantly higher complication rate then their subsequent fertility may be irrevocably compromised to avoid inadequate treatment in a much smaller number of women.

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Vulvodynia and selective IgA deficiency. Case reports

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Case reports

Patient no. 1

A 24-year-old nulliparous woman had suffered from pruritus vulvae and vulvodynia for 6 years. Symptoms had started with first sexual intercourse and were aggravated by coitus. Topical treatment brought no benefit. *Candida* species had been isolated from vaginal swabs on several occasions, but had readily responded to treatment with anti-fungal agents. At the time of referral, she was not using any drug or topical medication. She had no family history of skin problems or allergies. She was prone to upper respiratory tract infections. Physical examination revealed no abnormalities. The vulva, vagina and cervix appeared normal, with no discharge. There were no *Trichomonas*, acid-fast bacteria or fungi in the vaginal smear. The vulvar and cervical swab yielded no growth of common bacteria, gonococci, *Mycoplasma hominis, Haemophilus,* etc. Cytopathic effects of the vaginal fluid on HELA human fibroblasts were not seen and *Chlamydia* organisms were not detected. The vulvar biopsy showed no abnormality. Laboratory tests excluded anaemia, metabolic, hepatic and renal disorders. Hormone levels (17-β oestradiol, progesterone, total and free testosterone) maintained the pulsatory activity of a normal menstrual cycle. A diagnosis of 'vulvodynia' was made.

Patient no. 2

A 30-year-old nulliparous woman complained of perineal burning aggravated by micturition and coitus. She was taking oral contraceptives. In the last 2 years *Candida* organisms had been isolated from a vaginal swab on two occasions. There was no family history of similar disorders. Since infancy she had repeatedly suffered from pharyngitis and sinusitis. Clinical and laboratory data provided no explanation for her gynaecological symptoms. Repeated cultures of urine were sterile. The vulvar biopsy was normal. In the absence of any significant local finding, a diagnosis of vulvodynia was made.

Because of the respiratory symptoms, the immunological status of these two women was explored (Table 1).

Discussion

The two patients presented the typical clinical syndrome called vulvodynia (McKay 1988). It is an intense itching or burning vulva without laboratory and histological abnormal findings in the low genital and urological tract. Vulvodynia is a puzzling condition, described by sufferers as unbearable, often causing serious psychological problems. In our two patients a selective IgA deficiency, both in serum and in different secretions, was found. This is the most common immunological deficit, with a prevalence between 1:300 and 1:3000, depending on ethnic and geographical variations (Melamed *et al.* 1987). Affected persons may be totally asymptomatic (Plebani *et al.* 1986) but more often they suffer from recurrent sinus and respiratory tract infections (Plebani *et al.* 1986; French & Harrison, 1986), malabsorption (Wood *et al.* 1987), atopy, rheumatoid arthritis. The lack of secretary IgA causes defects at the mucus barrier level, with low capacity for bacterial opsonization (Gorter *et al.* 1987) and failure to block dietary antigens (Rosen *et al.* 1986). Despite many

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Table 1. Immunological characteristics

	Patient 1	Patient 2	References values
Blood*			
Leucocytes (10^3/ml)	3630	3600	4000–9000
Lymphocytes (10^3/ml)	1016	864	1500–3500
Total T (CD3) (%)	60	62	60–70
T Helper (CD4) (%)	46	44	40–50
T Suppresor (CD8) (%)	29	26	20–30
IgG (mg/dl)	1770	1800	800–1800
IgA (mg/dl)	<7·4	<7·4	90–450
IgM (mg/dl)	163	180	70–280
Saliva*			
IgG (mg/dl)	4.3	3	
IgA (mg/dl)	<0·5	<0·5	
IgM (mg/dl)	<0·5	<0·5	
Vaginal fluid†			
IgG (mg/dl)	6·2	7	
IgA (mg/dl)	<0·5	<0·5	
IgM (mg/dl)	<0·5	<0·5	

* Values expressed are the mean of three samples.
† Values expressed are the mean of three samples taken in the three phases of the ovarian cycle, see text for reference values.

experimental models (Usala *et al.* 1989; Wira & Sandoe 1980; 1987), IgA function in the female genital tract has not been extensively investigated. Many different proteins contribute to the local defensive mechanism in cervico-vaginal secretions: lysozyme, proteinase inhibitors and complement. IgM is rarely detectable but IgG and IgA are present in significant amounts, reported mean values being 20 mg/dl and 14 mg/dl respectively (Govers & Girard 1972). Immunoglobulin levels vary considerably with the hormonal cycle, the lowest concentration occurring during the luteinizing hormone peak (Schumacher *et al.* 1977), when IgA may be undetectable (Usala *et al.* 1989). It is rather difficult to associate different levels of IgA in vaginal fluid with specific diseases. In our patients, IgA deficiency could have favoured an altered local response to infection or allergens, which left a form of persistent dysaethesia (McKay 1989) without permanent tissue lesions. We suggest that the immunological status of the woman should be investigated, once a diagnosis of vulvodynia has been made. This syndrome has been little studied and IgA deficiency may be an important associated factor.

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ADONIS 030654569100154S

Placenta accreta and myotonic dystrophy. Two case reports

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Case reports

Patient no. 1

This 34-year-old woman was thought to be unaffected by myotonic dystrophy until 1983, when she was 27 years old (*vide infra*). There had been no relevant family history.

She had had miscarriages in 1974 and 1980. In 1982 a forceps delivery was necessary for second stage delay and a healthy 3·70 kg female infant was born. There was a large post-partum haemorrhage (PPH) of over one litre from an atonic uterus. Under general anaesthesia large pieces of adherent placenta were removed from the uterine cavity.

The next pregnancy in 1983 was uneventful until antepartum haemorrhages occurred at 27, 29 and 31 weeks. There was polyhydramnios but no fetal abnormalities were detected on ultrasound scan.

Rupture of the membranes occurred at 32 weeks and a 1·83 kg female infant was born spontaneously Once again there was a PPH and a difficult manual removal of the placenta. The placenta was 'unusually adherent and ragged', and 2 litres of blood were lost.

The infant had severe respiratory distress, talipes and reduced respiratory and limb movements. She was unable to swallow and it was felt there was a 'neuromuscular problem'; the infant died at 48 h.

In view of a possible diagnosis of myotonic dystrophy in the infant, the patient was investigated and the condition diagnosed by electromyography. Her mother was also found to have myotonic dystrophy.

In her next pregnancy (the diagnosis of myotonic dystrophy had now been made) labour was induced because of abdominal pain. At artificial rupture of the membranes there was fresh vaginal bleeding and a 'tongue' of placenta could be felt posteriorly. As there was heavy antepartum haemorrhage, a caesarean section was performed under general anaesthesia and a live female infant was born in good condition, weighing 2·75 kg. This child is alive and well.

However, there was a placenta accreta and severe haemorrhage necessitated hysterectomy. Histological examination showed chorionic villi in the myometrium (placenta increta).

The patient made a satisfactory physical recovery but became depressed.

Patient no. 2

This 29-year-old woman had been diagnosed as having myotonic dystrophy since age 12 years. The gene had probably passed through the paternal side of the family. Her grandfather had died at age 27 under general anaesthesia. Her father, two paternal uncles and a brother are all affected.

After a miscarriage at 16 weeks gestation in 1982, she had a normal delivery at term (in 1983) of a 2·65 kg female infant. At this delivery there was a PPH of 1500 ml associated with a relaxed uterus. The child was not affected by myotonic dystrophy and is alive and well.

In 1984, at 36 weeks gestation, there was an intrauterine death of a 2·22 kg female infant. The post-mortem showed 'marked joint and suture laxity' and it is probable that this infant was affected. Again the placenta was retained and a manual removal required. It was noted that 'the placenta was very adherent'.

In 1986, at 37 weeks gestation, there was evidence of asymmetrical intrauterine growth retardation. She was delivered by elective caesarean section under spinal anaesthesia for breech presentation and growth retardation. A

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1·94 kg female infant was born in poor condition. There was leg deformity and talipes. Again a PPH occurred and the placenta was densely adherent to the anterior uterine wall. This was a partial placenta accreta but haemostasis was achieved. The infant was severely affected with myotonic dystrophy and died at the age of 6 months with pneumonia.

A further pregnancy occurred in 1989 with a new partner. The pregnancy was complicated by anti-Kell and anti-D antibodies, but cordocentesis showed the fetus to be Kell and D negative. An ultrasound scan showed a Grade III placenta praevia and at 35 weeks the patient was admitted for rest. Preterm labour occurred after 2 days without antepartum haemorrhage. Caesarean section was performed under epidural anaesthesia and a 2·1 kg male infant was born in poor condition with similar defects to the previous infant.

Despite epidural anaesthesia and a placenta praevia, bleeding was not excessive, but there was severe placenta accreta and severe haemorrhage occurred on attempting to remove the placenta. A hysterectomy was performed. The histological examination confirmed placenta accreta.

Discussion

Myotonic dystrophy is an autosomal dominantly inherited disorder, the principal features of which are progressive muscle dystrophy, failure of the muscles to relax and the classic myopathic facies. The condition can affect several organ systems: cardiopulmonary (e.g., conduction defects, pneumonia and respiratory failure), gastrointestinal and renal.

The risks of myotonic dystrophy and pregnancy are well recorded in terms of risks to the fetus and newborn and mother, such as miscarriages (Shore & MacLachlan 1971), preterm delivery and neonatal death (Dunn & Deirker 1973), and deterioration of myotonic dystrophy (Hopkins & Wray 1967). Neither of our patients had deterioration of myotonic dystrophy during any of the pregnancies.

There have been 21 reported cases of myotonic dystrophy in pregnancy (Jaffé *et al.* 1986) and four of these involved PPH (Hopkins & Wray 1967, Shore & MacLachlan 1971, Webb *et al.* 1978, Jaffé *et al.* 1986) and one reported placenta accreta (Sarnat *et al.* 1976). In our two patients each pregnancy was complicated by either a PPH, difficult manual removal of the placenta and, in their final pregnancies, a severe degree of placenta accreta which necessitated hysterectomy. The deep implantation causing accreta may be due to a functional abnormality of uterine muscle (Shore & MacLachlan 1971).

Both our patients had other risk factors for placenta accreta such as previous caesarean section and placenta praevia. However, as each of their pregnancies had been complicated by a PPH and 'adherent placenta', it is likely that the myotonic dystrophy was a causal factor in their placenta accreta.

Women with myotonic dystrophy who are contemplating pregnancy should be advised of the risks of an affected fetus, the high perinatal loss, of worsening of the condition during pregnancy and the risk of PPH and possibly placenta accreta.

Prenatal diagnosis should be feasible in the future as the gene has been located on chromosome 19 and further DNA markers have recently become available. If it can be confirmed that the fetus is unaffected, then pregnancy could continue with the necessary counselling and precautions taken with regard to severe haemorrhage in the third stage of labour.

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Ovarian necrotizing vasculitis causing major intra-abdominal haemorrhage after IVF. Case report and literature review

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Case report

A 35-year-old woman underwent ovarian super-ovulation for in vitro fertilization (IVF) therapy after 3 years infertility associated with tubal and teratospermic factors.

Since the menarche at 13 years of age, this patient had been oligomenorrhoeic, with menses occurring every 5–12 weeks. Relevant aspects of her medical history were a severe episode of acute salpingitis in 1984, resulting in a left salpingectomy, and mild asthma, requiring intermittent bronchodilator therapy.

After initial investigations for infertility in 1987, which showed a patent right tube; a 12-month course of clomiphene resulted in ovulation, but not conception. Serum prolactin, FSH, LH and androgen levels were all within normal limits. She and her partner subsequently embarked on IVF therapy.

In their first attempt, follicular stimulation was achieved after suppression with a LH-RH agonist (500 µg buserelin for 3 days in the early follicular phase) followed by human menopausal gonadotrophin (hMG) (three ampoules of Pergonal daily for 10 days). This had followed a hormonal withdrawal bleed induced by norethisterone. Ovarian ultrasound on day 2 of the cycle was unremarkable. Five oocytes were collected from the five follicles >10 mm in diameter. Three oocytes were recovered laparoscopically from the right ovary. However, as laparoscopic access was poor on the left side, the two oocytes in the left ovary were collected transvaginally under ultrasound control. The maximal pre-ovulatory oestradiol concentration, being on the day of hCG administration, was 583 pg/ml and the maximal LH level was 1·3 iu/ml. Three cleavage stage embryos were replaced in the uterus, and the patient was discharged well on the second post-ovulatory day. She was given intramuscular progesterone (Gestone 50 mg daily) for luteal support.

On the ninth day after oocyte recovery, the patient experienced the sudden onset of severe abdominal pain and collapsed outside the clinic. She was pale and hypotensive, with generalized abdominal tenderness, guarding and rebound. She was resuscitated, and then underwent laparotomy. During this procedure, 4·5 litres of very heavily blood stained fluid were recovered from the peritoneal cavity. The right ovary was enlarged, but otherwise unremarkable. Multiple bleeding sites were identified on the enlarged left ovary. Haemostasis could only be achieved by an oophorectomy.

Pathology

The ovary was enlarged (4·8 × 2·8 × 2·6 cm) with focal irregularity of the ovarian capsule which was covered by clotted blood. Slicing revealed a brown grey gelatinous and mucoid cut surface, studded with several large cystic corpora lutea.

The entire ovary was then examined microscopically. The most interesting histological finding was the presence of a florid necrotizing vasculitis affecting small to medium sized blood

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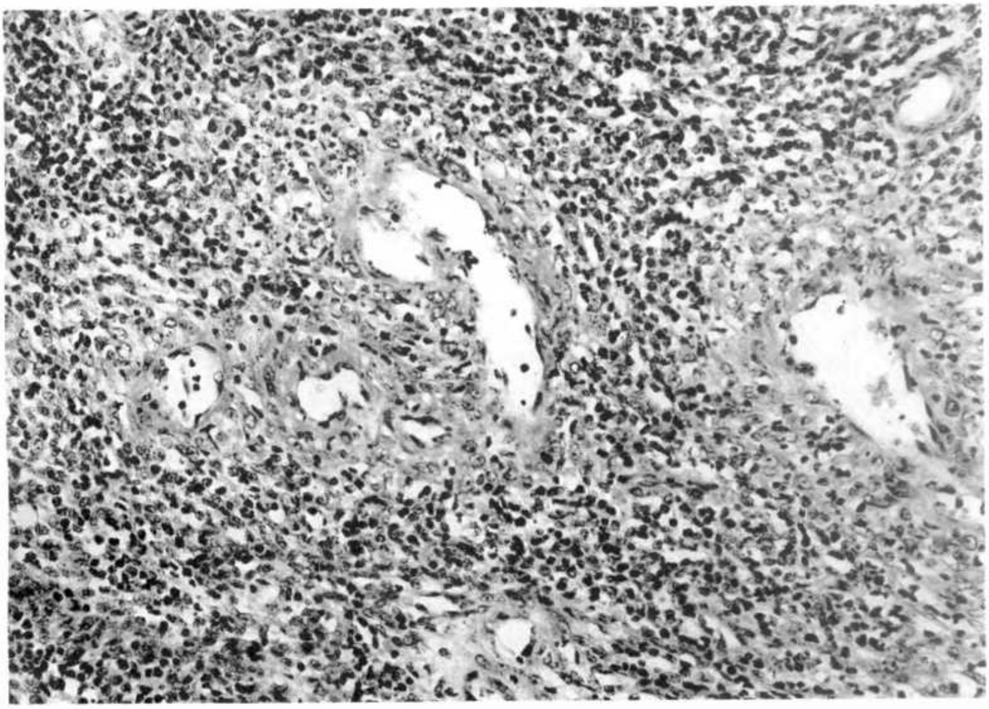

Fig. 1. Ovarian stroma heavily infiltrated by inflammatory cells. Blood vessel walls are also infiltrated and all except the small vessel in the upper right corner show extensive fibrinoid necrosis. (H-E ×200).

vessels, including arterioles, capillaries and venules, within the ovarian medulla. Many vessels showed circumferential fibrinoid necrosis in their walls, mainly subintimal in position. Some vessels contained karyorrhectic nuclear debris. The surrounding ovarian stroma was oedematous, focally haemorrhagic and infiltrated by eosinophils, neutrophils, lymphocytes, macrophages and plasma cells. Eosinophils were particularly numerous. Immunohistochemical stains showed that the majority of infiltrating lymphocytes were T-cell type. No granulomas were seen. The vasculitic changes were focal; the ovarian cortex and some areas of medulla being entirely spared. Enlarged corpora lutea bearing a prominent granulosa layer were also identified well away from the site of the bleed. There was no evidence of trophoblastic tissue nor any evidence of products of conception.

Auto-antibody screening, including anti-nuclear antibody, mitochondrial antibody, smooth muscle antibody, gastric parietal antibody and thyroid auto-antibodies were all negative.

The patient made an uneventful recovery and returned home on the fifth post-operative day. Eighteen months later she remains well.

Discussion

Massive intra-abdominal haemorrhage is an infrequent but well-recognized complication of IVF. This usually follows ovarian, parametrial or pelvic vascular trauma in the early post-operative period. Haemorrhage from a corpus luteum cyst or an ectopic gestation is well known in the weeks following IVF. However, haemorrhage from an ovary, showing the changes of florid acute necrotizing fibrinoid vasculitis, has not been reported previously.

Ovarian necrotizing vasculitis has been reported both in association with polyarteritis nodosa, and as an isolated finding in routine gynaecological surgery, especially when this involves the cervix, uterus or oviduct. Wilansky *et al.*, (1980) found only two examples of ovarian necrotizing vasculitis involving the female genital tract in a series of 11 women. Six of these were gathered over a 5-year period from 12 000

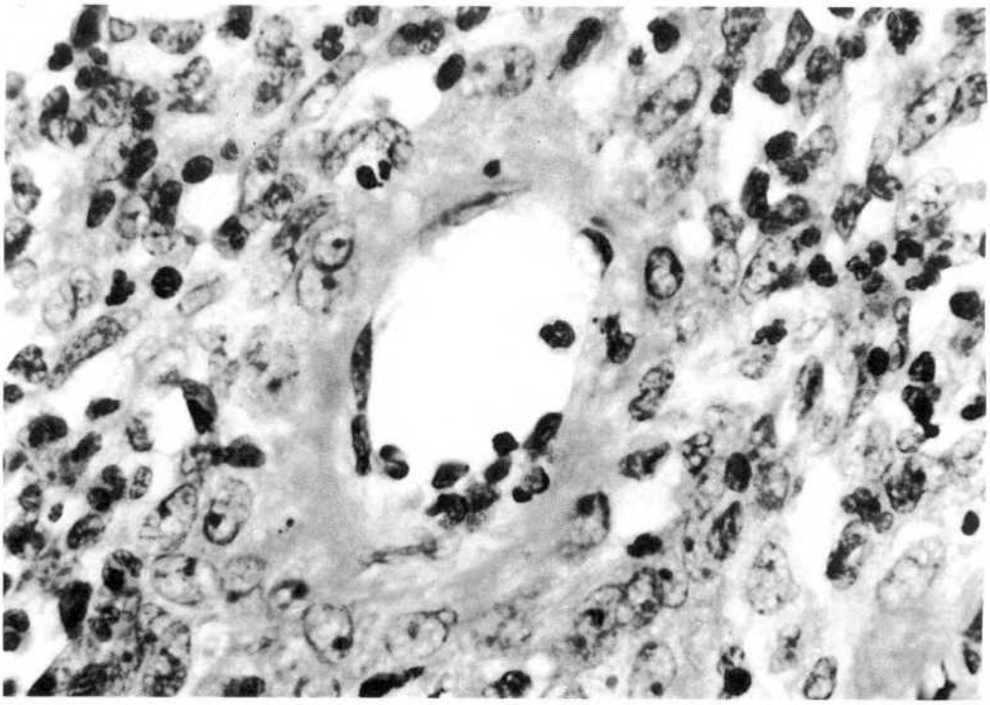

Fig. 2. Detail of a small blood vessel showing circumferential 'smudgy' fibrinoid necrosis of its wall and infiltration by inflammatory cells. (H-E ×800).

gynaecological specimens. This emphasizes the rarity of these findings.

Von Wegener (1952) first established that polyarteritis nodosa may involve the female genital tract. Piette *et al.* (1987) described a woman with systemic polyarteritis nodosa with declining general health and a large, firm uterus, who had a hysterectomy. Patalano & Summers (1961) reported five cases of uterine and six of ovarian arteritis found at autopsy in 17 women with systemic polyarteritis nodosa.

Plaut (1951) proposed that necrotizing vasculitis may be asymptomatic and localized to one organ. He reported 88 cases of incidental necrotizing arteritis of the appendix in 6574 appendices surgically removed. Isolated necrotizing vasculitis has also been reported in the skin (Ruiter 1958), the gall bladder (Bohrod & Bodon 1970) and the spinal cord (Feasby *et al.* 1975). From a review of the literature (Wilansky *et al.* 1980, 11 cases; Ansell *et al.* 1974, 10 cases; Crow & McWhinney 1979, 4 cases; Fetissof & Lansac 1980, 1 case; Lin 1978, 1 case), 27 cases of asymptomatic necrotizing vasculitis were found in routine histopathological studies following gynaecological surgery. None developed systemic disease, although the follow-up period was variable.

An association of necrotizing vasculitis with drug ingestion (especially penicillin), has been proposed (Wilansky *et al.* 1980; Irey 1976). However, Mullick (1979) found no evidence of necrotizing vasculitic lesions in 30 patients with drug related vasculitis. An Arthus-type reaction following cervical cone biopsy or inflammation with possible introduction of a hapten has been suggested by Kniker (1972). In a murine model, necrotizing lesions occurred following small doses of intravaginal acetone, with and without 20-methylcholanthrene (Campbell & Yang 1965), or with prolonged exposure to supra-pharmacological levels of oestrone (Cutts 1966). These may be hypersensitivity reactions.

Our patient had neither symptoms nor signs of a systemic vasculitis. Her general drug exposure was limited to occasional bronchodilator therapy and those drugs used for ovarian follicular hyperstimulation and luteal support. To date, no report has implicated the gonadotrophins or LHRH analogues in necrotizing vasculitis.

However, it remains possible that ovarian hyperstimulation or follicular aspiration may have triggered the necrotizing vasculitis. In support of a hypersensitivity mechanism was the presence of numerous eosinophils in the ovarian inflammatory infiltrate. These cells are well recognized for their predominance in many classic drug-induced hypersensitivity reactions. Alternatively, these factors may have provoked bleeding in an ovary with antecedent vasculitic changes.

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Imaging of pulmonary endometriosis by immunoscintigraphy. Case report

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Case report

A 36-year-old woman presented in 1989 with cyclical low abdominal pain and haemoptysis. She was first seen in 1980 with right iliac fossa pain. Minimal pelvic endometriosis was found at laparoscopy and was confirmed histologically; she was treated with danazol. In 1982, a repeat laparoscopy showed minimal scarring from old endometriosis. Her pain persisted despite further treatment with progestogens and a gonadotrophin releasing hormone agonist. Two laparotomies were performed in 1983–84 to divide pelvic adhesions; no further macroscopic evidence of endometriosis was found.

She first developed cyclical haemoptysis and left-sided pleuritic pain in 1986. A ventilation perfusion scan and bronchoscopy were normal. Pleuroscopy showed a macroscopically normal left pleural surface but on random biopsy there was microscopic evidence of chronic inflammation; pleurodesis was not performed. A clinical diagnosis of pulmonary endometriosis was made. Her symptoms gradually resolved without treatment but returned in 1988. She was treated with a combined oral contraceptive, taken continuously, but she then developed daily haemoptysis and breakthrough vaginal bleeding. In 1990, she had a total abdominal hysterectomy and bilateral salpingo-oophorectomy because her symptoms became very severe.

In the week before surgery, immunoscintigraphy was performed as described previously (Kennedy *et al.* 1990): 50 MBq ^{111}In-labelled monoclonal antibody OC-125 F(ab')$_2$ fragments (CIS, UK) were given by slow intravenous injection. Abdominal, pelvic and chest views were taken 24 and 48 h after the injection with a General Electric Maxi Camera 400T, fitted with a medium energy collimator and interfaced to a PCS 512+ computer (Nuclear Diagnostics) with MSC multi-user gamma 11 software. Each view was acquired over 5 min on a 128 × 128 pixel matrix using 20% and 15% energy windows centred on the 172 and 247 KeV peaks of ^{111}In respectively. Uptake was diffuse in the pelvis and there was a discrete area of uptake in the left lower chest (Fig. 1).

At operation, both ovaries were densely adherent to bowel and the broad ligaments. The left ovary contained an 8 cm diameter 'chocolate' cyst; histology confirmed endometriosis. Only one further episode of haemoptysis occurred in the 6 weeks after the operation. She was subsequently treated with transdermal 17β-oestradiol because of marked menopausal symptoms: intermittent haemoptysis recurred but to a lesser degree.

Discussion

Pulmonary endometriosis is a rare condition that

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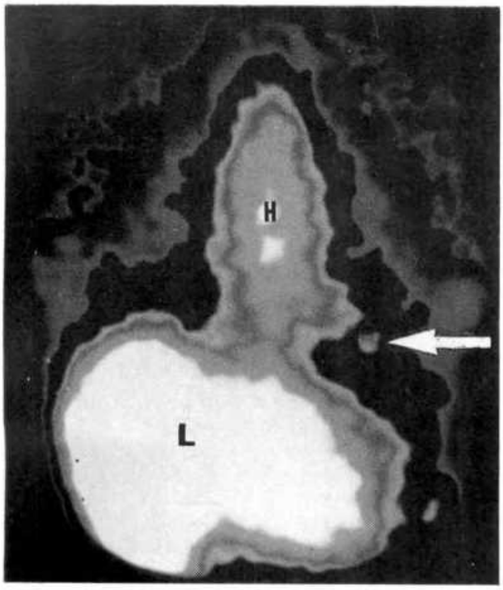

Fig. 1. Anterior chest digital image taken 24 h after injection of ^{111}In-labelled OC125 showing uptake in the left lower chest (arrow) in a patient with pulmonary endometriosis. H = heart blood pool; L = liver uptake.

presents with pleuritic pain, pneumothorax, haemothorax or haemoptysis concurrent with menstruation. The diagnosis is usually confirmed by bronchoscopy or thoracotomy. We report a case of pulmonary endometriosis imaged by immunoscintigraphy.

Immunoscintigraphy in gynaecology has previously been used almost exclusively for imaging ovarian malignancy (Chatal *et al.* 1987). There is one case report of metastatic gestational choriocarcinoma in the lung detected by an ^{131}I-labelled monoclonal antibody (SF9·3) raised against embryonal testicular cancer (Wahl *et al.* 1987).

We recently reported that ovarian endometriosis can be imaged using radiolabelled monoclonal OC-125 fragments directed against the antigen CA-125 (Kennedy *et al.* 1988) which is expressed on endometriotic tissue (Barbieri *et al.* 1986). Peritoneal endometriosis can similarly be imaged and uptake is enhanced if pelvic adhesions are also present (Kennedy *et al.* 1990).

This is the first report of the use of immunoscintigraphy to detect extra-pelvic endometriosis. In this case the diagnosis of pulmonary endometriosis was made on clinical grounds in the absence of histological evidence. The diagnosis still has not been proven but simultaneous uptake in the pelvis and chest is highly suggestive, as it the relation between oestrogen status and the occurrence of haemoptysis.

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ADONIS 030654569100157X

Raised serum CA 125 preceding the diagnosis of carcinoma of the fallopian tube: two case reports

ANN PRYS DAVIES, ANDREW FISH, ROBERT WOOLAS, DAVID ORAM

Case reports

Patient no. 1

A 52-year-old woman volunteered to participate in a multi-modal screening programme for ovarian cancer in asymptomatic postmenopausal women at The London Hospital (Jacobs *et al.* 1988). She had had one child but was now postmenopausal. Serum CA 125 was determined using the Abbot Laboratory CA 125 radioimmunoassay. An abnormal level was defined as >30 U/ml (Bast *et al.* 1983). Her initial CA 125 level in venous blood was elevated at 43·7 U/ml. Consequently real-time pelvic ultrasonography (transabdominal) was performed in accordance with the study protocol. This showed both ovaries to be of normal volume and morphology. No abnormality was noted.

She was followed up by 3 monthly serum CA 125 measurements, again in accordance with the study protocol. The serum level remained mildly elevated at 32·2, 35 and 38 U/ml at 3, 6 and 9 months respectively.

At 11 months after her initial CA 125 measurement she developed lower abdominal discomfort. A repeat ultrasound scan identified a 7 cm solid left-sided pelvic mass. At laparotomy she was found to have a carcinoma of the left fallopian tube and a hysterectomy, bilateral salpingo-oophorectomy and omentectomy was performed. Histological examination confirmed a poorly differentiated papillary adenocarcinoma of the left fallopian tube (Stage I).

At 6 weeks after surgery, having received pelvic irradiation, the serum CA 125 level was 15·22 U/ml.

Patient no. 2

A 53-year-old woman had also volunteered to participate in the ovarian cancer screening programme. She was postmenopausal and had two children. She had had a left oophorectomy in 1968 (age 32 years) for benign pathology.

The initial serum CA 125 level was raised at 57·4 U/ml. The right ovary identified on ultrasound measured 3·2×4×2 cm (giving a volume of 13·3 ml) but pelvic examination was normal. In view of the above findings, the procedure was repeated 3 months later. The serum CA 125 concentration had increased to 154·45 U/ml and the right adnexa measured 3·9×3·4×4 cm, with a volume of 27·7 ml.

At laparotomy a primary cancer of the right fallopian tube with ovarian metastases was discovered. A hysterectomy, right salpingo-oophorectomy, omentectomy and pelvic lymphadenectomy was performed. Histology confirmed an endometrioid adenocarcinoma of the fallopian tube. The uterus, omentum and nodes were free of disease.

At 6 weeks after operation her serum CA 125 level was 12·8 U/ml.

Discussion

Primary carcinoma of the fallopian tube is a rare condition with an incidence of 0·3% of genital tract cancers (Population Census and Surveys Cancer Statistics 1983). In its early stages carcinoma of the fallopian tube is quiescent or produces non-specific symptoms such as abdominal pain or classically a watery vaginal discharge (tubae hydrops profluens). The condition is seldom diagnosed pre-operatively. This was illus-

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trated by Pfeiffer *et al.* (1989) in a retrospective study of 52 cases of carcinoma of the fallopian tube. They reported that in not a single case was the diagnosis made in the pre-operative period.

We report examples of carcinoma of the fallopian tube diagnosed in women who had volunteered to participate in an ovarian cancer screening programme for asymptomatic women. In both the serum level of the tumour-associated antigen CA 125 was elevated prior to diagnostic surgery.

CA 125 has been defined by a murine monoclonal antibody OC 125. It is expressed by cells derived from the embryonic Mullerian duct and coelomic epithelium. Serum antigen levels are elevated in both benign and malignant conditions such as endometriosis, pelvic inflammatory disease, during the first trimester of pregnancy, and in association with cancer of the ovary, colon, endometrium and breast (Jacobs & Bast 1989). CA 125 has been most widely studied in association with the detection and monitoring of ovarian cancer. However, in view of its lineage it is not surprising that CA 125 is expressed by carcinoma of the fallopian tube and tissue sections have stained positive to CA 125 (Kabawat *et al.* 1983). Niloff *et al.* (1984) reported raised serum CA 125 in four women with recurrent cancer of the fallopian tube (range 76 to 8740 U/ml). Similar findings were obtained by Lootsma-Miklosova *et al.* (1987) having monitored six women with advanced fallopian tube cancer with serial serum CA 125 measurements.

In our two patients raised serum CA 125 concentrations were noted 11 and 3 months before the occurrence of symptoms and the subsequent diagnosis of carcinoma of the fallopian tube. In retrospect it is possible that the diagnosis might have been made earlier had repeat ultrasonography (employing a transvaginal probe) been performed at more frequent intervals.

Carcinoma of the fallopian tube should be considered as a possible, albeit rare, diagnosis in women with an elevated serum CA 125 and/or an identifiable adnexal mass. In such instances serial serum CA 125 levels may be used to monitor the progress of the disease or the response to adjuvant therapy and as an early indicator of relapse.

Acknowledgments

We wish to thank Mr M. Kettle FRCOG, for allowing us to report on his patient, Mrs A. E.

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SHORT COMMUNICATIONS

Pre-eclampsia and anti-phospholipid antibody

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An association between the antiphospholipid syndrome and pre-eclampsia was suggested by Branch *et al.* (1988) who reported that one-third of women with pre-eclampsia occurring before 34 weeks gestation had high titre anticardiolipin antibody. The antiphospholipid syndrome may occur as a primary syndrome in patients with no apparent underlying disease, being associated with thrombosis, thrombocytopenia and fetal loss. It is characterized by the presence of an antiphospholipid antibody, generally detected either by coagulation assays for lupus anticoagulant or by enzyme-linked immunoassay for the closely-related anticardiolipin antibody. Two patients in whom the antiphospholipid syndrome may have been mistaken for pre-eclampsia were described by Kilpatrick *et al.* (1989). They proposed the existence of hypertensive disease of pregnancy characterized by anticardiolipin antibody and distinct from 'true' pre-eclampsia. Faux *et al.* (1989), however, found that anticardiolipin antibody levels during both hypertensive and pre-eclamptic pregnancy were similar to those in normal subjects and they emphasized the difficulty of defining a normal range.

We used an enzyme-linked immunoassay validated by an international workshop (Harris *et al.* 1987) to measure anticardiolipin antibody in the sera of 20 women with proteinuric pre-eclampsia and 20 control women matched for parity, age within 5 years, and gestational stage within 13 days. The mean gestational age at sampling for the women with pre-eclampsia was 203·5 (SD 19, range 175–245) days. The control women were sampled at a mean gestational age of 204·3 (SD 18, range 170–239) days. All the pre-eclamptic patients had reversible hypertension and proteinuria, i.e., a diastolic blood pressure of ⩾110 mm Hg, the average maximum being 184·8 (SD 17)/118·6 (SD 5·5). The range in the systolic blood pressures was 160–220 and in the diastolic pressures 110–130. The patients had a proteinuria of ⩾1 g/24 h (mean 4·3, SD 2·5, range 1–90 g/24 h). Anticardiolipin antibody levels were defined using GPL and MPL units for IgG and IgM respectively, these being equivalent to the cardiolipin binding activity of 1μg/ml of an affinity purified IgG/IgM ACA from a standard serum. Sera were also analysed for antibodies to nuclear and smooth muscle antigens by immunofluorescence and Western blots (Taylor *et al.* 1988a).

Results and discussion

All positive findings were within the low positive range, i.e., 5·8–20 GPL and 5·4–21 MPL. Positive IgG anticardiolipin antibody occurred in five cases and eight controls and IgM anticardiolipin antibody in three cases and one control (Table 1). Of the seven cases having either IgG or IgM anticardiolipin antibody or both, four had matching controls with positive anticardiolipin levels. No sera in either group had antinuclear antibodies, smooth muscle antibodies or antibodies to the ribonucleoproteins Ro, La, Sm or nRNP.

There is evidence that anticardiolipin antibodies are associated with fetal loss (Harris *et al.* 1986). They may be effective at various levels in the reproductive process since they seem to be associated with both unexplained infertility (Taylor *et al.* 1989) and endometriosis (Gleicher *et al.* 1987). The pathogenic role of anticardiolipin antibody and stimulus to antibody production are undefined and Faux *et al.* (1989)

Table 1. Anticardiolipin antibody (ACA) levels in women with pre-eclampsia and matched controls

Pre-eclamptic patients		Matched controls	
IgG ACA (GPL units)	IgG ACA (MPL units)	IgG ACA (GPL units)	IgG ACA (MPL units)
4·7	<1·0	3·1	3·2
3·2	1·4	8·5*	2·4
4·8	5·6*	8·9*	4·0
<3·0	1·8	7·6*	2·0
4·0	1·8	5·1	7·2*
7·7*	3·3	7·5*	3·4
4·4	2·7	4·7	2·6
7·0*	3·4	7·8*	2·6
7·4*	3·2	5·5	3·4
5·5	1·8	5·5	2·6
9·5*	4·4	7·7*	5·4
4·4	2·9	7·0*	2·0
4·2	<1·0	5·1	3·4
4·8	3·6	4·8	2·5
12·5*	15·2*	5·8	2·2
5·2	<1·0	4·2	1·5
4·3	3·6	5·8	2·8
5·7	1·8	10·4*	5·0
4·4	6·0*	5·5	<1·0
3·4	2·8	5·4	4·3

* Low positive ACA levels

suggested that low titres may be elicited as a general response to tissue injury rather than specifically associated with pregnancy. Although there is preliminary evidence that development of anticardiolipin antibody may sometimes be a secondary phenomenon related to surgical intervention (Taylor *et al.* 1988b), a transient significant rise in antibody levels has been reported during normal gestation (Cowchock *et al.* 1984), possibly as an immune response to the developing fetoplacental unit. Clinical effects of the antiphospholipid syndrome may be mediated by binding of antiphospholipid antibody to phospholipids in endothelial cell membranes with a resultant decrease in prostacyclin production. The antagonist thromboxane would then predominate causing vasoconstriction, platelet aggregation and intravascular thrombosis. Since Spitz *et al.* (1988) have shown that low-dose aspirin given to women at high risk for pregnancy-induced hypertension suppresses the production of thromboxane by platelets, efficacy of this treatment may be related to amelioration of the action of anticardiolipin antibody. In recent years, various types of reproductive failure have come to be considered as having an autoimmune component ranging from unexplained infertility to fetal loss. There is evidence that patients with pre-eclampsia and those suffering from unexplained recurrent miscarriage share common immunogenetic markers (Christiansen *et al.* 1990). However, the apparent physiological increase in anticardiolipin antibody associated with normal pregnancy and the results reported here emphasise the difficulty of ascribing significance to an individual finding of raised levels in pregnant women.

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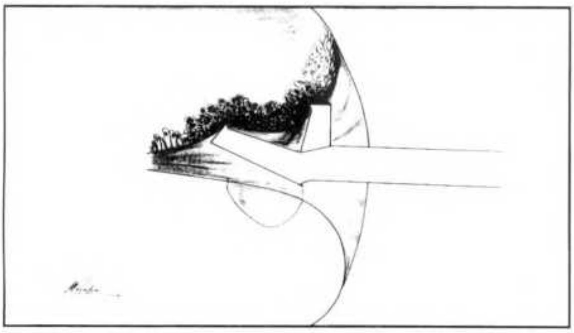

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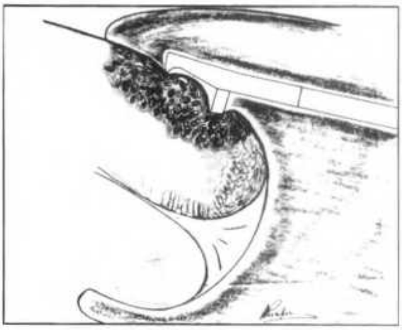

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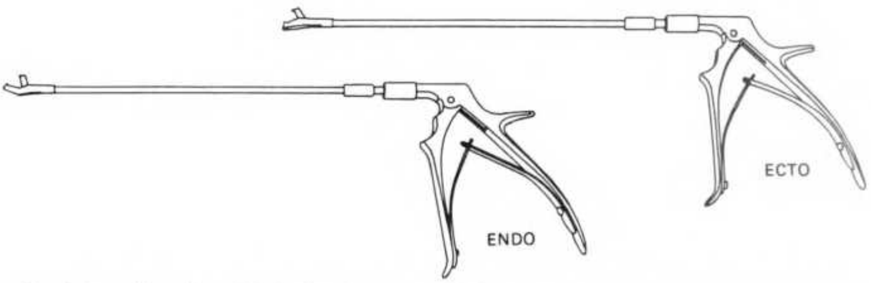

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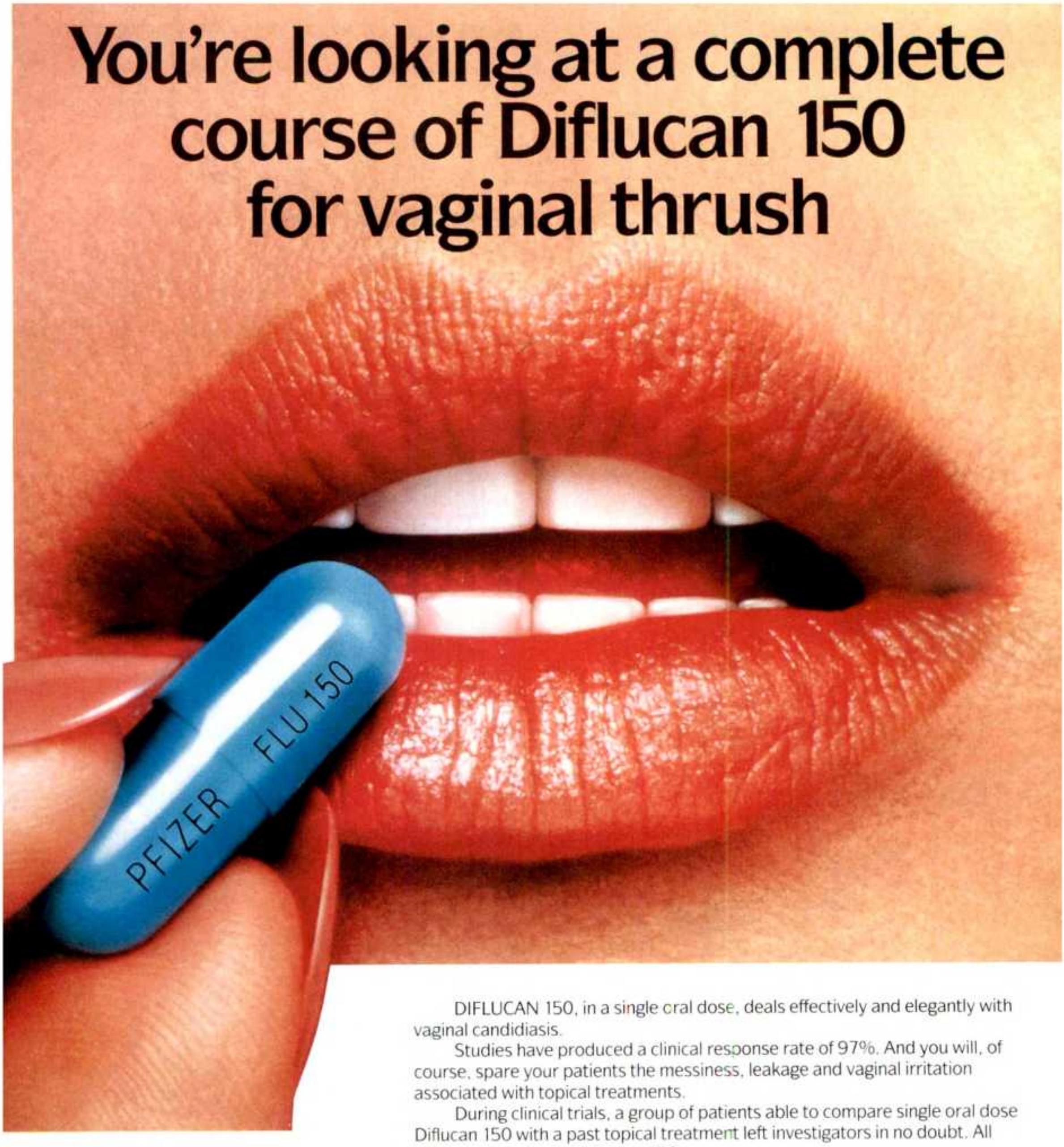

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ADONIS 030654569100159P

CORRESPONDENCE

Hormone implants and tachyphylaxis

Dear Sir,

Although entitled 'Hormone implants and tachyphylaxis', the paper by Garnett *et al.* [*Br Obstet Gynaecol* (1990) **97**, 917-921] does not address the issue of tachyphylaxis.

According to Webster's Medical Dictionary, 'tachyphylaxis' is defined as 'diminished response to later increments in a sequence of applications of a physiologically active substance'. The central issue with oestradiol implants is a clinical scenario in which some patients return, at decreasing intervals after implantation, complaining that their symptoms have recurred. Re-implantation based upon symptom recurrence can eventually lead to the paradox whereby women with supraphysiological levels of oestradiol also complain of typical oestrogen-deficiency symptoms. In this circumstance, re-implantation is of limited benefit and eight of the patients in our original report (Gangar *et al.* 1989) derived symptomatic relief for periods of only 3–9 weeks after another implant. In our paper, we also stated that the 'optimal management in these cases . . . is not known'. We recommended that further oestrogens be withheld, an approach described by Garnett and colleagues as 'wrong, and in severely depressed patients may be dangerous'. However, these authors did not propose an alternative strategy for this unfortunate group of women. The lack of an agreed strategy and the need to judge each case on its own merits with the prescription of oestrogens in patients with severe depression has been discussed (Gangar *et al.* 1990).

We applaud the effort of Dr Garnett and his co-workers in trying to determine the prevalence of supraphysiological levels of oestradiol in women receiving serial implants, but we cannot agree with their conclusion that this occurs in only 3%. We challenge their use of 1750 pmol/l as the upper limit of the physiological range observed during the reproductive era when most laboratories, including the one used by them, quote 1300 pmol/l for the peak value attained during the peri-ovulatory phase. The use of a reference range from another laboratory is not valid and this fundamental flaw negates any meaningful conclusions being drawn about the prevalence of supraphysiological oestradiol levels and also that of tachyphylaxis from their analyses. If the 1300 pmol/l value quoted by the laboratory who performed their assays is applied as the upper limit of the physiological range, then by our calculations approximately 15% of their patients had supraphysiological oestradiol levels when they returned complaining of a recurrence of symptoms. Because of the way the data have been presented, we cannot estimate the prevalence of tachyphylaxis in their patients.

According to Dr Garnett *et al.* 'Subsequent implantation was performed at the return of symptoms, usually at 6 months, when the dose would generally be reduced to 50 or 25 mg oestradiol'. In their group of 23 postmenopausal women with plasma oestradiol values about 1750 pmol/l, only three were receiving implants at intervals of 6 months (the other 20 were receiving therapy more frequently), none was receiving 25 mg implants and only nine were receiving 50 mg implants. Thus, we agree that this group appears to require more oestrogen than the rest of their patients. The authors argue that this group represents a minority of women who need supraphysiological oestradiol values to control symptoms, and that a history of previous psychiatric disease or premature, surgical menopause is a strong predictor. Obviously, this is an important observation for clinical practice but, in the absence of a valid group for comparison, no firm conclusions can be drawn. The high incidence of psychiatric history and premature surgical menopause in this group may also be present in the general population of women attending their Clinic, and no data were provided to help resolve this question. We would like to see confirmatory data which demonstrate that the incidence of psychiatric history or premature surgical menopause in women with supraphysiological oestradiol levels is significantly greater than that in women with oestradiol values around or below the ovulatory peak. If such a difference is demonstrated then the authors' hypothesis is confirmed: the converse also applies.

We agree that oestrogen replacement therapy is a major development in preventative medicine. Oestrogens can be administered by a variety of routes and all have relative merits and disadvantages Compared with oral and transdermal therapies, subcutaneous implants achieve higher plasma oestradiol values with a proportion of patients exhibiting plasma concentrations within and above the peri-ovulatory range 4–6 months after last implantation. Although the authors state in their Discussion that '50 mg oestradiol given at 6-month intervals . . . will not lead to supraphysiological oestradiol levels', their Table 1 shows that two women, so treated, had oestradiol values of 1860 and 1920 pmol/l.

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Authors' reply

Dear Sir,

Our only area of agreement with Gangar & Whitehead is that tachyphylaxis is an inappropriate description of this phenomenon. However, this was the term used in their original paper (Gangar *et al.* 1989) and it is difficult to understand the logic of their protest

We reported the oestradiol levels in 1388 women having long-term implant therapy who were seen during one year (Garnett *et al.* 1990), whereas Gangar *et al.* (1989) described 12 women collected during an unknown time and from an unknown database with no clinical details. Their criticisms and demands for clarification of our paper seem somewhat audacious.

In our paper, the number of women with various oestradiol levels at the time of return of symptoms were shown in a histogram. If readers wish to accept a different upper level of normality appropriate calculations can easily be made from the data for a specific plasma oestradiol level. We should not slavishly adopt the normal values of any laboratory, particularly if one's own considerable experience is of finding normal untreated patients having values outside these limits.

There remains some debate about the true prevalence of this finding but an estimation from our large database from a busy specialist practice is more helpful than a 'show of hands' at a menopause meeting (Gangar *et al.* 1990)

We are currently studying the residual psychiatric problems of our patients and intend to compare personality/addiction profiles of patients with supraphysiological and of those with normal oestrogen levels. There is no doubt that depressed patients are referred selectively to our clinic. These end up with high oestradiol levels because in the first place, we treat patients with resistant or cyclical depression with higher doses of oestradiol than those with only vasomotor symptoms or the problems of atrophy.

Similarly we treat patients with severe premenstrual depression with 200 µg Estraderm patches (Watson *et al.* 1989) or 100 mg oestradiol implants with the sole objective of elevating the plasma oestradiol levels from normal to high constant levels and have reported significant improvements of severe premenstrual symptoms with these regimens. Of our 38 patients with supraphysiological oestradiol levels 15 were suffering from premenstrual tension which had failed to respond to other treatments.

We repeat that 50 mg oestradiol implants administered every 6 months do not result in high oestradiol levels. Although we reported two women with high oestradiol levels after receiving 50 mg at their last implant, both had been treated for 8 years with regular larger doses (never more than 100 mg) for their depression. Both had been able to discontinue antidepressants for the first time after 10 years of previous use.

We have shown previously that climacteric symptoms return while plasma oestradiol levels are still in the normal range and that repeated implants have a cumulative effect on plasma oestradiol levels (Cardozo *et al.* 1984; Brincat *et al.* 1984). Does this matter? We think not as the only clear difference is one of benefit, in that the incremental increases in bone density of spine and the proximal femur are related to the levels of oestradiol reached (Studd *et al.* 1990; T. J. Garnett *et al.* unpublished data). Savvas *et al.* (1988) reported that high oestradiol levels attained after 8 years of implant therapy were associated with greater bone density than was observed after 8 years of oral therapy. A 75 mg oestradiol implant increased vertebral bone density by 8% in 1 year compared with an untreated reference group (T. N. Garnett unpublished data) and oral and transdermal oestrogens increased bone density at the same site by up to 2–3% above that in an untreated group (Stevenson *et al.* 1990). It may be that the literal interpretation of tachyphylaxis (tachy=fast, phyllaxis=protection) is, afterall, very appropriate for the rapid protection that implants give the skeleton.

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ADONIS 030654569100160J

A morphological and immunological study of human placental bed biopsies in miscarriage

Dear Sir,

In their recent paper [*Br J Obstet Gynaecol* (1990) **97**, 984-988] Michel *et al.* suggest that some women with non-viable pregnancies miscarry because they have low levels of 'suppression'. This suppression is defined by the depressant effect of supernatant from placental bed biopsy specimens on lymphocyte proliferation. They go further to suggest that the suppressor factor(s) may be produced by uterine cells with large granules. They therefore conclude that the low level of suppression they found in the non-viable pregnancies could be explained by the diminished numbers of these cells as found in their placental bed biopsies. We wish to suggest that these conclusions are unsubstantiated and misleading, and we offer what are simpler but we believe more plausible explanations for their findings:

(1) Many factors deriving from the placenta during pregnancy are known to have immunosuppressive activity: these include steroids, α-fetoprotein and prostaglandins to name but a few. A biopsy specimen from the placental bed is likely to contain some of these factors. It is obvious that these factors are more likely to be at higher concentrations in viable than in non-

viable pregnancies (unembryonic or missed miscarriages). Therefore, it should not be surprising that placental bed biopsies from non-viable pregnancies have diminished suppressor activity: it is the non-viability of these pregnancies that accounts for the diminished suppressor activity, rather than the converse. While reports from murine studies suggest that an immunosuppressive factor related to transforming growth factor-β (TGF-β) may be produced by uterine granulated cells (Clark *et al.* 1988), simple extrapolation to humans may be misleading, given the significant differences between murine and human placentation.

In addition, the test of suppresor activity as described in their previous paper (Michel *et al.* 1989) is really not discriminatory enough to suggest the precise source or the nature of the active factor(s). Placental bed biopsies contain a multitude of cellular and humoral elements, any or none of which could be the source of the factor(s).

(ii) A combination of the idea that intrauterine immunoregulation may be fundamental for normal feto-placental development and the finding of granulated lymphocytes that appear to predominate in the uterus has led to a plethora of publications on these lymphocytes [see King & Loke (1990) for a review with an extensive bibliography]. Although a fair amount is now known about their lineage and phenotype, the simple truth of the matter is that their function is not known. They appear to be under hormonal regulation since they increase progressively in the luteal phase, reaching a maximum around the sixth post-ovulatory day, and then dying a day or two pre-menstrually if fertilization and implantation does not occur, but if pregnancy occurs they are present throughout the first trimester (King *et al.* 1989). Thus it is much more plausible to conclude that in non-viable pregnancies, the diminished number of granulated lymphocytes is due to a suboptimal hormonal milieu i.e., again their diminished number is a consequence of the failed pregnancy and not the converse.

Therefore, the diminished suppressor activity and the diminished number of granulated cells are likely to be independent variables which are both due to a suboptimal hormonal milieu that must surely exist in non-viable pregnancies. The authors also admit that sampling errors may explain some of their observations: even allowing for experience and high resolution ultrasonography, biopsing the placental bed at such early gestations must be technically very difficult. Given that they are dealing with such small numbers, the impact of sampling error is likely to be very important.

Finally, progress in science can only be made if, among other things, those in the forefront of research discard ideas as and when they become obsolete. It is therefore disconcerting to find Michel *et al.* in their introduction boldly stating that women who fail to make a humoral immunological response to the placental antigens of the fetus tend to miscarry. It is unclear what humoral responses they are referring to. In their discussion they admit that others have shown that antipaternal cytotoxic antibodies are unlikely to be important in maintaining a pregnancy, since their occurrence is not universal, and they tend to occur late in pregnancy (Regan 1988). So could they be alluding to the wholly unsubstantiated theories of the so-called trophoblast cross-reactive (TLX) antigens and anti-idiotype networks, in which case they should perhaps be less affirmative in their assertions?

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Authors' reply

Dear Sir,

Manyonda & Pearce criticise the hypothesis that an antibody response by the mother to placental antigens is important for successful pregnancy and that a defect in this response is a cause of recurrent miscarriage. However, women with recurrent miscarriage immunized with their husbands blood lymphoid cells who develop antipaternal antibody enjoy prolonged protection against miscarriage (Mobray *et al* 1987). Failure to detect antibody in all who have a successful pregnancy does not invalidate the hypothesis. The antibody detected by complement dependent killing of husbands cells *in vitro* is only a correlate of successful pregnancy, MLR blocking antibodies are a better correlate, but a different antibody, bound to a distinct antigen on trophoblast, appears most significant (Jalali *et al.* 1989; Clark & Blair 1991). The latter is absent in the serum of women who miscarry, but has been detected in all women with a successful pregnancy after immunization (Clark & Blair 1991). Serum antibody against trophoblast has been detected in 77% of women in the first trimester (Davies & Browne 1985) and could be present at serum titres too low to measure (Voisin & Chaouat 1974). Agammaglobulinaemic women have had successful pregnancies, but their serum IgG levels are seldom zero The regular gammaglobulin injections given to agammaglobulinaemic women may suffice to prevent miscarriage (Clark & Daya 1991). Mice with recurrent abortion have deficient suppression by granulated lymphocytes in decidua and immunization prevents abortion and boosts suppression (Clark *et al.* 1987 and 1990). Suppression is mediated by a factor related to transforming growth factor beta-2, and a similar suppressor factor is deficient in the decidua of some women with recurrent miscarriage (Clark *et al.* 1991*a*). Preliminary data from a collaborative study with Dr Judith Bulmer indicate that a subset of granulated lymphoid cells may produce the TGF-beta-2 factor *in situ*. Trophoblast can activate lymphoid cells in luteal phase endometrium to release suppressor factor (Daya *et al.* 1989) and our most recent data using fresh trophoblast membrane (Jalali *et al* 1989) show that IgG must be present (Daya *et al* 1991). We are not aware of any convincing evidence that progesterone, alphafetoprotein, or prostaglandins mediate suppression *in utero* in the first trimester of human pregnancy.

As noted above, human decidual granulated lymphoid cells are functionally heterogeneous, consistent with surface marker and morphologic data (Christmas *et al.* 1990; Michel *et al.* 1989). A subset can be activated to kill trophoblast (King & Loke 1990) and we have hypothesized subnormal suppression facilitates this activation. In the absence of activation stimuli, pregnancy could succeed without any suppression (or antibody), but we doubt this is common. Although all of the functions of granulated lymphocytes in decidua may not be known, some are.

Placental bed biopsy may not be representative of all areas of the implantation site (Michel *et al.* 1989), but sampling error is unlikely to account for differences between women who miscarry and control donors. Although failing pregnancy and hormonal factors (Regan *et al.* 1990) could to some extent account for a low frequency of some types of granulated cells in decidua, pregnancy failure does not appear to cause subnormal suppression (and subnormal numbers of TGF-beta-2^+ cells) in decidua. Our current studies indicate that it is a subset of women who have subnormal suppression. Those who miscarry with normal levels of suppression may have a genetic defect, as has been shown in the mouse (Clark *et al.* 1991*b*).

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ADONIS 030654569100161W

The clinical presentation of women with human immunodeficiency virus infection

Dear Sir,

There is likely to be greater demand for medical and counselling services for HIV infected women as the HIV prevalence rate in this group increases. In a recent paper by Kell *et al.* [*Br J Obstet Gynaecol* (1991) **98**, 103–104] different reasons were cited for the variation in rates (18-60%) for uptake of HIV antibody tests after counselling in antenatal clinics. We would concur with the suggestions that the type of counselling offered and uncertainty surrounding the outcome of HIV on pregnancy may militate against testing. It is noteworthy that in France (Moatti *et al.* 1990) and Sweden (Larsson *et al.* 1990) social acceptability of testing among antenatal clinic attenders is high. In our own HIV testing clinic, we have found an uptake rate of between 93% and 99% (Bor *et al.* 1991; Squire *et al.* 1991) although admittedly this is with a general medical population rather than antenatal clinic attenders. One difficulty with *a posteriori* hypothesis testing is that there is no access to the decision-making process of patients who attend for counselling and therefore insufficient data from which to explain why some patients do not go on to be tested. By offering the test to 'at risk' women, many infected women are not tested (Kransinki *et al.* 1988) and some doctors may then suggest that women should be tested without first being counselled and without their consent. We would argue that the acquisition of basic HIV test counselling skills (Miller *et al.* 1990) and the setting up of more convenient HIV testing facilities (e.g., same day or 24-h results) is preferable to the short-cuts some doctors may be tempted to make.

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British Journal of Obstetrics and Gynaecology
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ADONIS 030654569100162B

Vulval reconstruction by free tissue transfer

Dear Sir,

The case report by Srivastava & Maxwell [*Br J Obstet Gynaecol* (1991) **98**, 98-100] gives hope for the large number of African and Arab women, who have been subjected to female circumcision, better called genital mutilation, in childhood. Far from dying out, this practice still affects millions of women, although it has usually been shrouded in silence, and attempts to eradicate the practice have met with little success (Ladjali & Toubria 1990).

In Britain there is now a well organized campaign against the sexual mutilation of young girls growing up in this country, which also gives help to those women suffering from the effects of the procedures. There is also now an increasing awareness, particularly among the Somali communities, and some are now asking if there is a way of reconstructing the vulva.

Although the report referred to a vulva which had been distorted by disease, the pre-operative appearance was not dissimilar from the effects of infibulation. It also demonstrated the important point that not only was the vulva more anatomical in its appearance after surgery but intercourse became possible once again

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British Journal of Obstetrics and Gynaecology
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BOOK REVIEWS

The Baby Machine, Reproductive Technology and the Commercialisation of Motherhood, edited by Jocelynne A. Scott. Green Print, London, 1990, 342 pages, £8.95

By the time you get to the second page of this Australian book, you pretty well have its measure. Women, the editor sternly tells us, do not benefit from advances in genetic and reproductive engineering. After all, she tells us, most technological reproduction programmes are fostered, run and controlled by men. *Quod erat demonstrandum*—what need to say more? Unfortunately there are a further 300 pages on much the same line, delivered by 11 contributors, with varying degrees of polemic. The general theme is the wickedness of the male species and in particular, 'white male pharmocrats', who, if I follow it correctly, are judged to be engaged in a vast reproductive experiment at women's expense.

Feminist rhetoric apart, there are a good many reasons to feel concerned about the way in which the fertility services are developing and the chapter entitled 'Commercialisation of Reproductive Technologies' highlights some of these. Given its consumer, rather than feminist approach, this chapter works well and develops some interesting themes, such as the way in which the possibilities of patentable research, rather than patient welfare, may direct future university infertility work as funding becomes scarce.

The scandalous way in which success rates are massaged by some IVF clinics deserves exposure but is not given as much prominence here as one might have expected. Many of the contributors explore the theme of infertility treatment being a sort of merry go round—easy to get on, but perilously hard to get off—although none of them seem to advance any suggestions as to how this situation might be resolved. And whilst great play is made of the women as pawns theme, with infertility reducing their ability to make choices, a basic truism has been ignored. It's much easier to enrol women in yet another hopeless programme, than it is to say 'this is the end of the line'. Perhaps we ought to be teaching future generations of doctors less about the far flights of reproductive science, and rather more about how to communicate with their patients.

Vivienne Parry

Baillière's Clinical Obstetrics and Gynaecology International Practice and Research Vol 3/No 3, September 1989, Laparoscopic Surgery edited by C. J. G. Sutton. Baillière Tindall London, 1989, 429–686, with figures and tables, annual subscription UK £40, single issue £18.50

With the growing interest in 'minimally invasive surgery', this volume is a timely addition to the series on Clinical Obstetrics and Gynaecology. Although there is an understandable bias towards the use of lasers, the book covers all the major areas of current interest, with chapters written by recognized authorities from both Europe and the USA.

The volume starts with a chapter tracing the history of endoscopy and laparoscopic surgery. Kurt Semm (West Germany), arguably the father of operative laparoscopy, gives the reader an almost tutorial like chapter on instruments and techniques developed in his unit in Kiel over the past 15–20 years. Appropriately, Semm is followed by Maurice Bruhat (France), the other major force in gynaecological laparoscopy and the pioneer of the use of lasers. This theme is continued by international experts including Chris Sutton (UK), Jacques Donnez and Michelle Nissole (Belgium), James Daniell (USA) and Jorg Keckstein (West Germany) who expand on the use of not only the CO_2 laser but also fibre-optic systems. Later in the volume, however, Diamond (USA) warns against the uncritical acceptance of these newer treatment methods and it is evident that the superiority of lasers compared with other techniques has still to be proven. With this in mind, Meyer and DeCherney (USA) discuss the various laparoscopic procedures that can be employed for the treatment of ectopic pregnancy. The new techniques of double-optic laparoscopy and endoovarian surgery are dealt with by their originators, Brosens and Puttemans (Belgium). Laparoscopic sterilization by Filshie (UK) is perhaps a surprise chapter, while that on documentation by Wamsteker (Holland) is full of useful practical information. Fittingly, the book ends with Harry Reich (USA), a pioneer of more radical laparoscopic techniques, including a brief mention of what should be called laparoscopically assisted hysterectomy and pelvic lymphadenectomy.

With the exception of cost comparisons, this volume is comprehensive, whets the appetite, and provides both basic and more advanced information. It should convince the sceptics that the scope of endoscopic intervention is limited only by our ingenuity. All gynaecologists (as well as theatre nurses and administrators) should read it!

Adam Magos

Human Sex Determination. An Historical Review and Synthesis by Ronald Wells. Riverlea Publications, Tharwa, Australia, 1990. 244 pages, £15.00

While the testes produce equal numbers of spermatazoa bearing X and Y chromosomes, on average more boys are born than girls. The reason for this and the fact that the ratio varies has long fascinated epidemiologists, and has raised the possibility that if the circumstances that cause the variation could be defined it might be possible for individual couples to choose the sex of a planned child.

There is an immense, but scattered literature on sex determination, and Dr Wells has pursued it with a marvellous curiosity. He has assembled all the published epidemiological data, and many from unpublished population statistics, with a proper scepticism for those where birth registration may have been biased. Also, he has examined most of the possible physiological variables from the relation of coition to ovulation, the state of the cervical mucous, and the timing of orgasm during intercourse, to parent age, coital rates and the season of the year.

His main conclusion seems to be that an excess of male infants is positively related to the frequency of intercourse, and the book concludes with advice on maximizing the chance of having a male or female child.

The book is not just a comprehensive, critically discussed mine of information, it is a very entertaining read. Take this final paragraph from his advice section: 'It may be noted that nothing has been recommended above about douching before intercourse, coital positions, special diets, or for that matter about biting the wife's right ear and holding the husband's right scrotum during intercourse. If people have faith in or get pleasure from any of these or other harmless sophisticated sexual refinements, why not relax and enjoy them? However I am not aware of any objective evidence that they affect the sexes of resulting children'.

Highly recommended.

F. E. Hytten

Baillière's Clinical Obstetrics and Gynaecology, International Practice and Research. Medical Induction of Abortion, Vol 4 No 2, June 1990, edited by M. Bygcleman. Baillière Tindall, London, Philadelphia, 1990. 235–418 pages with figures and tables, £22.50 single issue, £49.00 annual subscription.

This volume follows a well recognized pattern already established in this excellent series. With a world authority as its editor it can be expected that the contributions will be authoritative and comprehensive. This is both its strength and perhaps, for a British readership, its weakness.

The opening chapter which gives a world-wide view of termination of pregnancy, highlights the varying availability of terminations throughout the world and therefore emphasizes the need for alternatives to surgical abortion in countries with inadequate medical facilities. This is followed by two sections on the biophysiology of uterine activity and cervical ripening and their relation to abortifacient drugs. There is an excellent critical chapter on post-coital contraception and the editor himself has written the section on termination of early pregnancy. This chapter includes a comprehensive review of the use of antiprogestogens in association with prostaglandins and contains sections on cervical ripening, intrauterine applications of abortifacients and the medical managements of abnormal pregnancies that concentrate on the use of prostaglandin analogues. The majority of these agents are unfortunately unavailable in the United Kingdom. This may, perhaps, engender a feeling of frustration among practitioners in this country when they are unable to utilize the techniques and regimens described. This volume may however act as a stimulus to encourage the wider availability of these drugs.

The final chapters on the acceptability of abortion techniques and the effect of termination on future reproduction are particularly relevant in view of the increasing need for abortion world-wide. As an overview of a developing aspect of our specialty this book can be thoroughly recommended.

Peter Stewart

Essential Medical Genetics, Third Edition, by J. M. Connor & M. A. Ferguson-Smith. Blackwell Scientific Publications, Oxford, London, Edinburgh, 1991. 259 pages with figures and tables, £12.95

The preface to this book states that it has been written for those to whom an understanding of medical genetics is important in their practice as clinicians, scientists, counsellors and teachers but, essentially, it remains an undergraduate textbook of human and clinical genetics and, as such, succeeds very well. Busy clinicians wanting to mug up on clinical genetics might do better to opt for Helen Kinston's 'ABC of Clinical Genetics' (BMA publications) and those whose practice impinges more regularly on genetic problems might want to carry as a prophylactic Peter Harper's 'Practical Genetic Counselling' (John Wright, Bristol), but for a good, solid grounding in medical gentics you can't beat Connor & Ferguson-Smith. The only serious competitor is Gelehrter & Collins 'Principles of Medical Genetics' (Williams & Wilkins), which is also an excellent book, and perhaps more 'grown-up' than Connor & Ferguson-Smith, but less well designed and light on clinical genetics.

There has been extensive revision since previous editions, and the text is up to date. The clinical chapters are particularly well illustrated for a textbook of this type and the chapters on basic genetics contain many useful diagrams that aptly illuminate the text. If I had to pick out something to criticize it would be the illustrations of translocated and inverted chromosomes during meiosis which I would have found difficult to follow, if I did not already understand the topic (which I only just about do). There are two self-assessment sections which are excellent and make me thankful my MCQ days are over.

If I was writing a 'Basics of . . .' or 'Introduction to . . .' Medical Genetics, with this sort of competition around, I'd be a depressed man.

Robin Winter

Books received some of which may be reviewed at a later date

Female Reproductive System (Systemic Pathology. Third edition Volume 6) edited by M. C. Anderson. Churchill Livingstone, Edinburgh, 1991. 488 pages, 511 illustrations, £80.00

Introduction to Clinical Reproductive Endocrinology by Gillian C. L. Lachelin. Butterworth Heinemann, London, 1991, 203 pages fully illustrated, £24.95

Contrast-Enhanced MRI of the Breast by Sylvia H. Heywang-Kobrunner: Karger, Basel 1990, 244 pages with figures and tables £35.70, DM 98, US $65.75

Progress in Perinatal Medicine (Life Science Series. Volume 9), edited by D. F. Hawkins, G. C. Di Renzo and E. V. Cosmi. Harwood Academic Publishers, Cooper Station, New York, NY, 1990, 349 pages with figures and tables. List price $95.00, Society price $60.00

Pathology for Gynaecologists Second edition by H. Fox and C. H. Buckley, Edward Arnold, Hodder and Stoughton, London, 1990, 304 pages, fully illustrated, £49.50

Medical Disorders During Pregnancy edited by William M. Barron and Marshall D. Lindheimer. Mosby Year Book, St Louis, 646 pages, with figures and tables, £57.00

Health Care of Women and Children in Developing Countries edited by Helen M. Wallace and Kanti Giri. Third Party Publishing Company, Oakland, California, 1990, 598 pages with figures and tables, $36.95

Atlas of Human Sperm and Morphology edited by Roelof Menkveld, R. James Swanson, E. E. Oettlé, Anibal A. Acosta, Thinus F. Kruger and Sergio Oehninger. Williams and Williams, Baltimore 1991, 121 pages fully illustrated, £100.00

Baillière's Clinical Rheumatology International Practice and Research—Pregnancy and the Rheumatic Diseases. Volume 4, Number 1, April 1990, edited by A. L. Parke. Baillière Tindall, London, 1990, 176 pages with figures and tables, UK annual subscription £41.00 single issue £22.50

The Climateric Hot Flush (Progress in Basic and Clinical Pharmacology Volume 6) edited by E. Schönbaum. Karger, Basel, 1991, 166 pages with figures and tables, £69.20, $127.25

Abortion and Afterwards by Vanessa Davies. Ashgrove Press, Bath 1991, 226 pages paperback, £6.99

Handbook of Obstetric Anaesthesia by A. S. Buchan and G. H. Sharwood-Smith, W. B. Saunders, London, 1991, 119 pages, £9.95

A Journal of Perinatal Care and Education

Birth

Editor: Diony Young, Geneseo, New York

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